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(54) Title: COMPOUNDS AND METHODS OF TREATING CELL PROLIFERATIVE DISEASES

(57) Abstract: The present invention relates to compounds and their uses, particularly in the pharmaceutical industry. The invention discloses compounds having anti-proliferative activities, as well as methods for treating various diseases associated with abnormal cell proliferation, including cancer, by administering said compounds. It further deals with pharmaceutical compositions comprising said compounds, more particularly useful to treat cancers.

COMPOUNDS AND METHODS OF TREATING CELL PROLIFERATIVE DISEASES

The invention relates to compounds and their uses, particularly in the pharmaceutical industry. The invention discloses compounds having anti-proliferative activities, as well as methods for treating various diseases associated with abnormal cell proliferation, including cancer, by administering said compounds. It further deals with pharmaceutical compositions comprising said compounds, more particularly useful to treat cancers.

Cancer is still one of the leading causes of death in developed countries, as cancer affects all ages, sexes, racial and ethnic groups. According to the American Association for Cancer Research, one out of five deaths in the US is caused by cancer. Worldwide, the most predominant cancer sites are lung (14%), prostate (13%), breast (11%) and colorectal (11%) (data obtained from the Cancer Statistic Branch, NCI).

Cancer rate is increasing in developed countries in spite of falling incidence of several cancers such as prostate cancer (due to detection programs) or lung cancer in men (due to prevention programs). Among the fastest increasing cancer rates are non-Hodgkin 's lymphoma cancer and melanoma (3% annual rise) in the US (The Annual Report to the Nation on the Status of Cancer, 1973-1997).

Unlike cancer incidence, cancer deaths have declined in developed countries. This is due in part to better therapy designs but also to prevention programs and better detection of some cancers at an earlier stage.

However, in spite of higher achievements in treatment and prevention of cancers, several improvements are awaited for:

- effective therapies for early stage cancer to reduce relapses,
- alternative therapies for curing tumors refractory to standards therapies,
- alternative therapies for curing metastatic cancers
- less toxic drugs, and
- better delivery systems.

Inhibitors of cell signaling pathways could represent such a new alternative therapy by addressing the first three issues, when used alone or in combination with standard chemotoxic drugs.

There are various receptors, enzymes and effector molecules involved in the biochemical pathways necessary for signal processing in a cell. These include small GTPases, which are monomeric guanine nucleotide-binding proteins of 20-25 kDa molecular mass, which function as molecular switches. They are "on" in the GTP-bound state and "off" in the GDP-bound state. Cycling between the active and inactive forms is controlled by several accessory proteins: the guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs) and GDP dissociation inhibitors (GDIs). The active GTP-bound GTPases interact with a variety of effectors proteins to produce their cellular effects.

Ras, the first GTPase discovered, gave rise to the Ras super family of GTPases. It is a key regulator of cell growth and is found in mutated oncogenic forms in a large number of human tumors. When specific residues in Ras are mutated, this protein becomes constitutively active (insensitive to GAP action) and causes cell transformation. The Ras oncoproteins are among the most potent mitogenic polypeptides known, and activating mutations of Ras are found in nearly one-third of all human cancers.

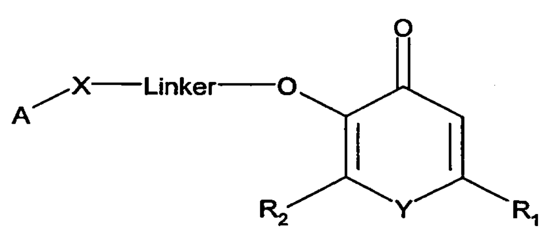
The Rho subfamily of GTPases is composed of 3 major subtypes, namely Rho, Rac, and Cdc42, which control actin cytoskeleton in distinct ways. Other major roles for the Rho proteins are the regulation of gene transcription (JNK and p38 mitogen-activated protein kinase, serum response factor, NFkB), cell cycle progression, and adhesion. Several Rho GTPases have been shown to play an important role in cell transformation.

U.S. Patent No. 4,590,201 discloses compound L651582, a cell signaling inhibitor. This compound inhibits proliferation and inflammation by affecting the

biochemical pathways necessary for signal processing in the cell. It is an indirect blocker of the effector enzymes which produce the second messengers necessary to induce growth.

The present invention now relates to the identification and characterization of a new class of compounds which present an anti-cell proliferation effect, more particularly on tumor cells. Without being bound by any theory, this effect is believed to be due to either an activity on cell signaling, as described above. In particular, as illustrated in the examples, compounds of this invention inhibit the oncogenic properties of the above family of proteins, potentially by impairing the nucleotide exchange. However, the anti-proliferative activity of the compounds of the present invention may not be restricted to cell signaling and to exclusive interaction with the members of the GTPases protein family. Advantageously, these compounds will inhibit or reverse malignant cell phenotypes in a wide array of human tissues, have little or no effect on normal cell physiology, will be highly active so that a limited number of treatments will be needed for each patient, and will have excellent bio availability and pharmacokinetic properties.

Accordingly, one aspect of the invention is to provide a compound having a general formula (I):

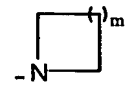


(I)

wherein:

R_1 is CH_2R_3 or COR_3;

R_2 represents a hydrogen atom or an alkenyl group containing from 3 to 6 carbon atoms;

R_3 is -OH, -OR_4, -SR_4, -NR_5R_6 , or  ;

R_4 represents a group selected from alkyl containing from 1 to 6 carbon atoms, a cycloalkyl group a radical –$CONR_5R_6$, aryl, a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero- atoms selected from oxygen, sulfur and nitrogen, heteroaryl, aralkyl, heteroaralkyl, alkanoyl or cycloalkanoyl from 2 to 6 carbon atoms, arylcarbonyl, heteroarylcarbonyl, arylalkanoyl and heteroarylalkanoyl ;

R_5 and R_6, independently from each other, are selected from a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

m is 2 or 3 ;

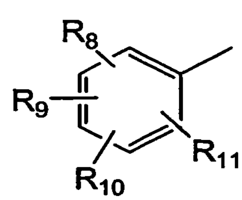
"linker" represents $(CH_2)_n$, wherein n represents an integer between 1 and 10 inclusive or a xylenyl group;

Y represents an oxygen atom, a sulfur atom or a radical -NR_7- ;

R_7, identical or different, is selected from a group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

- either :

X represents an oxygen atom, a sulfur atom or a radical –NR_7-;
A represents either a substituted phenyl group of formula



in which:

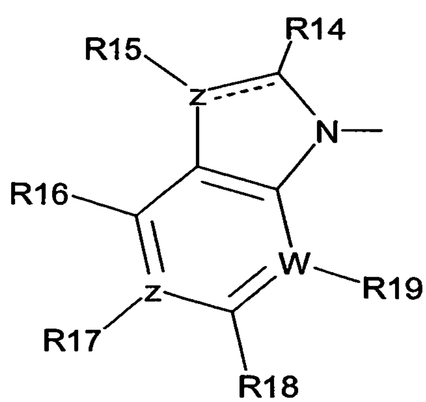
R_8, R_9, R_{10} and R_{11}, independently from each other, are selected from a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an alkenyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, a (C_1-C_{10})alkoxycarbonyl group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, a -NHCO(C_1-C_6)alkyl group, $-NO_2$, -CN, a $-NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group; preferably R_8, R_9, R_{10} and R_{11}, not being simultaneously hydrogen atom,

or alternatively two substituents, R_8 and R_9, may form together a mono- or poly-cyclic hydrocarbon group with the carbon atoms of the phenyl group they are attached and the two other substituents, R_{10} and R_{11}, are as defined above ;

or A represents a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero-atoms selected from oxygen, sulfur and nitrogen, said ring is bonded directly to X;

R_{12} and R_{13}, independently from each other, are selected in the group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

- or X-A represents a group of formula (II):



wherein :

R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, independently from each other, represent a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, an aryl

group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, $-NO_2$, -CN, a $-NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group, R_{12} and R_{13} being as defined above; alternatively, R_{14} and R_{15} may form together with the bond they are attached thereto a cycloalkyl group (preferably a cyclohexyl group) or an aryl group (preferably a phenyl group);

W represents a carbon or nitrogen atom;

Z represents a carbon or nitrogen atom;

With the provisos that:

- when X and Y are oxygen atoms, A is a phenyl group, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 5 and R_8 on the ortho position on the phenyl group vis-à-vis X is n-propyl group, then at least one R_9, R_{10} and R_{11} is different from hydrogen ;
- when X and Y are oxygen atoms, A is a phenyl group, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 5, R_8 on the ortho position on the phenyl group vis-à-vis X is n-propyl group, R_9 on the meta position vis-à-vis X is an hydroxyl group, and R_{10} on the para position vis-à-vis X is an acetyl group ; then R_{11} is different from hydrogen ;
- when X and Y are oxygen atoms, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 2 or 3, then A is different from a non-substituted naphthalene group;

its tautomers, optical and geometrical isomers, racemates, salts, hydrates and mixtures thereof.

In a particular embodiment, the compounds of the present invention present a genarl formula as defined as, with the further proviso that:
when X and Y are oxygen atoms, A is a phenyl group, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 5 and R_8 on the ortho position on the phenyl group vis-à-vis X is n-propyl group, then R_9, R_{10} and R_{11} are different from hydrogen.

The compounds of the present invention may have one or more asymmetric centers and it is intended that stereoisomers (optical isomers), as separated, pure or partially purified stereoiomers or racemic mixtures thereof are included in the scope of the invention.

The present invention also relates to pharmaceutical compositions comprising at least one compound as defined above in a pharmaceutically acceptable support, optionally in association with another active agent.

The present invention also relates to the use of a compound as defined above, for the manufacture of a medicament for the treatment of diseases associated with abnormal cell proliferation, such as cancers.

The present invention also includes methods of treating diseases associated with abnormal cell proliferation, such as cancers, comprising the administration to a subject in need thereof of an effective amount of a compound as defined above.

As will be further disclosed in this application, the compounds according to this invention have strong cell proliferation inhibitory activity and are effective at reducing or arresting growth of proliferating cells such as tumor cells.

Preferred embodiments

Within the context of the present application, the terms alkyl and alkoxy denote linear or branched saturated groups containing from 1 to 6 carbon atoms. An alkoxy group denotes an -O-alkyl group.

The alkyl groups may be linear or branched. Examples of alkyl groups having from 1 to 10 carbon atoms inclusive are methyl, ethyl, propyl, isopropyl, t-butyl, n-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, 2-ethylhexyl, 2-methylbutyl, 2-methylpentyl, 1-methylhexyl, 3-methylheptyl and the other isomeric forms thereof. Preferably, the alkyl groups have from 1 to 6 carbon atoms.

The cycloalkyl group is more specifically an alkyl group forming at least one cycle. Examples of cycloalkyl groups having from 3 to 8 carbon atoms inclusive are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl group may be optionally substituted.

The alkenyl groups may be linear or branched. Examples of alkenyl containing from 3 to 6 carbon atoms are 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and the isomeric forms thereof.

The term aryl includes any aromatic group comprising preferably from 5 to 14 carbon atoms, preferably from 6 to 14 carbon atoms, optionally interrupted by one or several heteroatoms selected from N, O, S or P (termed, more specifically, heteroaryl). Most preferred aryl groups are mono- or bi-cyclic and comprises from 6 to 14 carbon atoms, such as phenyl, α-naphtyl, β-naphtyl, antracenyl, or fluorenyl group.

The term aralkyl group generally stands for an aryl group attached to an alkyl group as defined above, such as benzyl or phenethyl.

The term mono- or poly-cyclic hydrocarbon group is understood to refer to hydrocarbon cyclic group having from 1 to 20 carbon atoms, optionally interrupted with one or more heteroatoms selected in the group N, O, S and P. Among such mono- or poly-cyclic hydrocarbon groups, cyclopentyl, cyclohexyl, cycloheptyl, 1- or 2-adamantyl groups, pyran, piperidine, pyrrolidine, morpholine, dioxan, tetrahydrothiophene, and tetrahydrofuran can be cited. The mono- or poly-cyclic hydrocarbon group may form with the phenyl group it is attached an aryl group, such as a α-naphtyl, β-naphtyl, or antracenyl group.

An alkanoyl group is a –CO-alkyl group, the alkyl group being as defined above.

The term arylcarbonyl group generally stands for an aryl group attached to a carbonyl group, the aryl group being as defined above.

The term alkoxycarbonyl group generally stands for an alkoxy group attached to a carbonyl group, the alkoxy group being as defined above.

The term 5- to 12- membered heterocyclic ring, preferably 5- or 6- membered heterocyclic ring, includes pyrrole, pyran, pyridine, furan, thiophene, pyrimidine, pyrazine, imidazole, thiazole, oxazole, indole, purine, benzo[b]furan, benzo[b]thiophene, isoquinoline, quinoline, 6,7-dihydro-5*H*-(2)pyridine, 1*H*-pyrazolo[3,4-b]pyridine, thienopyridine.

The groups specified above may be optionally substituted. More specifically, the alkyl, alkoxy, alkenyl, aryl, aralkyl, mono- or poly-cyclic hydrocarbon group, and the 5- to 12- membered heterocyclic ring may be optionally substituted with one or more groups selected from hydroxyl group, halogen atom, cyano group, nitro group, cycloalkyl group, ester (-COO(C_1-C_6)alkyl group), -OCO(C_1-C_6)alkyl group, amide (-NHCO(C_1-C_6)alkyl or -CONH(C_1-C_6)alkyl group), (C_1-C_{10})alkyl radical, (C_1-C_{10})alkoxy radical, mono- or poly-cyclic hydrocarbon group, C=O group, a -$NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group.

Preferably, R_{12} and R_{13} are hydrogen atom or ethyl group.

The xylenyl group is a dimethylbenzene radical, in particular the xylenyl group is the m-xylenyl, o-xylenyl or p-xylenyl group.

The trifluoro(C_1-C_6)alkyl group is preferably the trifluoromethyl group.

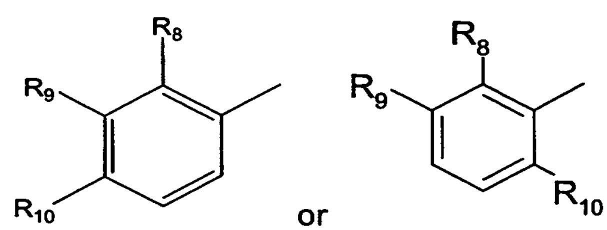
In a particular embodiment, when R_3 represents –NR_5R_6, preferably R_5 is a hydrogen atom and R_6 is selected from an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl.

In a particular embodiment, when R_3 represents $-OR_4$, wherein R_4 is NR_5R_6, preferably R_5 is a hydrogen atom and R_6 is selected from an alkyl group having from 1 to 10 carbon atoms, a cycloalkyl, an aryl and an aralkyl group, optionally substituted, especially substituted with halogen atoms and/or NO_2.

According to preferred embodiments, the compounds according to the invention correspond to general formula (I) wherein:

- X is oxygen or sulfur; and/or
- Y is oxygen; and/or
- linker is $(CH_2)_n$, wherein, n is from 4 to 7 inclusive or a xylenyl group (meta, para or ortho); and/or
- R_1 is $-CH_2OH$, $-CH_2$-O-benzyl, $-CH_2$-O-tetrahydropyran, $-CO_2H$ or -CO-NH-benzyl ; and/or
- R_2 is a hydrogen atom, a propen-1-yl group, a propen-2-yl group; and/or
- A is a substituted phenyl as defined above, a pyridine group (preferably pyridin-2-yl group), a furan or a thiophene group, optionally substituted.

In a preferred embodiment, when A is a substituted phenyl, the substituted phenyl presents the following formula :



In a particular embodiment, when A is a substituted phenyl as defined above, at least one of the substituents on the phenyl group is an halogen atom, more preferably chlorine.

A particular preferred group of compounds according to the present invention, are the compounds of formula (I) wherein A is a phenyl group substituted with at least two substituents simultaneously represent Cl.

In a particular embodiment, when A is a substituted phenyl as defined above, at least one of the substituents on the phenyl group is a halogen atom, an alkyl group (preferably propyl) or an alkenyl (preferably propenyl), a trifluoroalkyl group (trifluoromethyl group), $-NO_2$, -CN, an alkoxy group (preferably methoxy or butoxy, optionnally substituted with a cycloalkyl group (preferably cyclopropyl), an alkoxycarbonyl group (preferably $-COOC_2H_5$), a alkanoyl group (preferably acetyl), a $-NR_{12}R_{13}$ group, preferably wherein R_{12} is H and R_{13} is hydrogen or an alkyl group (more preferably ethyl group), or a $-NHCO(C_1-C_6)$alkyl group (preferably $-NHCOCH_3$).

Another particular preferred group of compounds according to the present invention, are the compounds of formula (I) wherein R_8 represents a hydrogen atom, a propyl group or an ethoxy group, R_9 and R_{10} represent a hydrogen atom, or an halogen atom, preferably chlorine, and R_{11} is a hydrogen atom.

In a preferred embodiment, when A is a substituted pyridine (preferably pyridin-2-yl), the pyridin is substitued with at least a halogen atom, preferably chlorine, and/or trifluoroalkyl (preferably trifluoromethyl).

In a preferred embodiment, when A is a substituted thiophene, the thiophene is substitued with at least a halogen atom, preferably bromine, and/or an alkoxycarbonyl group (preferably $-COOCH_3$).

In a preferred embodiment, when A is a substituted furan, the furan is substitued with at least one, or more specifically two, alkyl group (preferably CH_3).

In a preferred embodiment, when X-A represents a group of formula (II) as identified above,

- W and z represent a carbon atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}, or
- W represents a nitrogen atom, z represents a carbon atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}, or
- W and z represent a carbon atom and a single bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}, or
- W and z represent a nitrogen atom atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}.

In a more preferred embodiment, the compounds are of formula (I) where X-A represents a group of formula (II), wherein W and z represent a carbon atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}.

According to preferred embodiments, when X-A represents a group of formula (II) as identified above, the compounds according to the invention correspond to general formula (I) wherein :

- Y is oxygen ; and/or
- linker is $(CH_2)_n$, wherein, n is from 2 to 8 inclusive, preferably 5, or a xylenyl group (meta, para or ortho); and/or
- R_1 is $-CH_2OH$, $-CH_2OCONR_5R_6$, wherein R_5 is preferably H and R6 is preferably ethyl, cyclohexyl, phenyl, optionally substituted with halogen atom (preferably Cl) or with NO2, -CH2OCO-alkyl (preferably propyl), -CH2OCO-cycloalkyl (wherein preferably cycloalkyl is cyclohexyl), $-CH_2$-O-CO-benzyl, $-CH_2$-O-CO-aryl (wherein aryl is preferably phenyl or furan), $-CH_2$-O-tetrahydropyran, $-CO_2H$ or -CO-NH-benzyl ; and/or
- R_2 is a hydrogen atom, a propen-1-yl group, a propen-2-yl group.

In a particular embodiment, when X-A is the group of formula (II), R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, independently from each other, represent a hydrogen atom, a aryl group (preferably a phenyl group), an alkyl group (preferably a methyl

group), an alkoxy group (preferably a methoxy group), a halogen atom (preferably Cl or F).

In another particular embodiment, when X-A is the group of formula (II), R_{14} and R_{15} form together with the bond they are attached thereto a cycloalkyl group (preferably a cyclohexyl group) or an aryl group (preferably a phenyl group) and R_{16}, R_{17}, R_{18} and R_{19}, independently, represent preferably a hydrogen atom and/or an alkyl group.

In another particular embodiment, when X-A is the group of formula (II), R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19} represent a hydrogen atom.

When the compounds according to the invention are in the forms of salts, they are preferably pharmaceutically acceptable salts. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium,

methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol, etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, fonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane, etc. Mixture of solvents may also be used.

Specific examples of compounds of formula (I) which fall within the scope of the present invention include the following compounds :

5-[5-(4-Chlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[5-(3-Chlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[5-(3,4-Dichlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[4-(3,4-Dichlorophenyloxy)butyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[5-(4,5-Dichloro-2-propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[5-(2-Ethyloxyphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[6-(3,4-Dichloro-2-propylphenyloxy)hexyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[7-(3,4-Dichloro-2-propylphenyloxy)heptyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[9-(3,4-Dichlorophenyloxy)nonyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

2-(Benzyloxymethyl)-5-[5-(3,4-dichlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one

5-[5-(4-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

5-[5-(3-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

5-[5-(3,4-Dichlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

5-[4-(3,4-Dichlorophenyloxy)butyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

5-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

5-[5-(2-Ethyloxyphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

N-Benzyl-5-[5-(4-chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxamide

(E)-3-[5-(4-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)-3-[5-(3-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)-3-[5-(3,4-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)-3-[5-(3,4-Chloro-2-propylphenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)- 6-(Hydroxymethyl)-2-(propen-1-yl)-3-[5-(2-propylphenyloxy)pentyloxy]-4*H*-pyran-4-one

(E)- 3-[5-(4-Chlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(E)- 3-[5-(3-Chlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(E)- 3-[5-(3,4-Dichlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(*E*)- 3-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(*E*)- 2-(Propen-1-yl)-3-[5-(2-propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-6-carboxylic acid

2-Fluoro-4-[5-(6-hydroxymethyl-4-oxo-4*H*-pyran-3-yloxy)-pentyloxy]-benzonitrile (EHT 2904)

5-[5-(2-Allyl-4-chloro-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 5431)

5-[5-(4-Chloro-2-propyl-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 6152)

5-[5-(2-Allyl-3,5-dichloro-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 6978)

5-[5-(3,5-Dichloro-2-propyl-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT2991)

(*E*)-3-[5-(3,5-Bis-trifluoromethyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 5403)

(*E*)-3-[5-(3,4-Difluoro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 8307)

(*E*)-2-Fluoro-4-[5-(6-hydroxymethyl-4-oxo-2-propenyl-4*H*-pyran-3-yloxy)-pentyloxy]-benzonitrile (EHT 4112)

(*E*)-3-[5-(2-Allyl-4-chloro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 9226)

(*E*)- 3-[5-(4-Chloro-2-propyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 1405)

(*E*)-3-[5-(2-Allyl-3,5-dichloro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 6506)

(*E*)-3-[5-(3,5-Dichloro-2-propyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 9916)

2-Hydroxymethyl-5-(5-indol-1-yl-pentyloxy)-4*H*-pyran-4-one (EHT 6353)

Ethyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 1120)

Cyclohexyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 6231)

Phenyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 4902)

(4-Chloro-phenyl)-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2232)

(4-Nitro-phenyl)-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 5332)

Butanoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 1393)

Cyclohexanecarboxylic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2253)

Phenyl-acetic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2665)

Benzoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 6517)

Furan-3-carboxylic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 4167)

4-Chloro-benzoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 0078)

(*E*)-6-Hydroxymethyl-3-(5-indol-1-yl-pentyloxy)-2-propenyl-4*H*-pyran-4-one (EHT 7286)

5-(5-Indol-1-yl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7395)

5-(5-Phenylsulfanyl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 1414)

2-Hydroxymethyl-5-(5-phenylsulfanyl-pentyloxy)-4*H*-pyran-4-one (EHT 2939)

5-(5-Phenoxy-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6245)

2-Hydroxymethyl-5-(5-phenoxy-pentyloxy)-4*H*-pyran-4-one (EHT 1329)

5-[5-(5-Chloro-pyridin-2-yloxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0696)

5-[5-(5-trifluoromethyl-pyridin-2-yloxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 1171)

5-[5-(3,4-Dimethoxy-phenylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 3663)

4-Bromo-3-{5-[4-oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-thiophene-2-carboxylic acid methyl ester (EHT 4408)

3-Cyclopropylmethoxy-4-{5-[4-oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-benzoic acid ethyl ester (EHT 7565)

5-[5-(4-Butoxy-3-nitro-phenylamino)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5230)

5-[5-(4-Acetyl-3-ethylamino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9411)

N-(3-{5-[4-Oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-4-propyl-phenyl)-acetamide (EHT 7151)

5-[5-(6-Acetyl-3-ethylamino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7096)

5-[5-(2-Phenyl-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9013)

5-[5-(4-Acetyl-3-amino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5769)

5-[5-(2,5-Dimethyl-furan-3-ylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7976)

5-[5-(2,4-Dimethyl-pyrido[2,3-*b*]indol-9-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6448)

5-[5-(2-Methyl-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2427)

5-(5-Pyrrolo[2,3-b]pyridin-1-yl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8309)

5-[5-(5,6-Dimethoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5457)

5-[5-(6-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5235)

5-[5-(6-Chloro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8617)

5-[5-(4-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0091)

5-[5-(5-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8140)

5-[5-(2,4-Dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-*b*]indol-9-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7337)

5-[5-(3,4-Dichloro-phenylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0407)

5-[5-(5-Chloro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0823)

5-[5-(5-Fluoro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0533)

5-[5-(2-Methoxy-4-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9387)

5-[2-Indol-1-yl-ethoxy)-2-(tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 7599)

5-(3-Indoyl-1-yl-propoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 4283)

5-(4-Indol-1-yl-butoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5741)

2-Hydroxymethyl-5-(4-indol-1-yl-butoxy)-4*H*-pyran-4-one (EHT 3089)

5-(4-Indol-1-yl-(*trans*)-but-2-enyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6895)

2-Hydroxymethyl-5-(5-indol-1-yl-pentyloxy)-4*H*-pyran-4-one (EHT 6353)

5-(5-Indol-1-yl-hexyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2358)

5-(8-Indol-1-yl-heptyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8733)

5-(8-Indol-1-yl-octyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2271)

5-[5-(5-Chloro-indol-1-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 9238)

5-[5-(2,3-Dihydro-indol-1-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 8650)

5-[5-(6Chloro-purin-9-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 0248)

2-Hydroxymethyl-5-[5-(3-methyl-indol-1-yl)-pentyloxy]-4*H*-pyran-4-one (EHT 3065)

5-[5-(5-fluoro-indol-1-yl)-pentyloxy]-2-Hydroxymethyl-4*H*-pyran-4-one (EHT 9546)

5-[5-(6-chloro-indol-1-yl)-pentyloxy]-2-Hydroxymethyl-4*H*-pyran-4-one (EHT 9853)

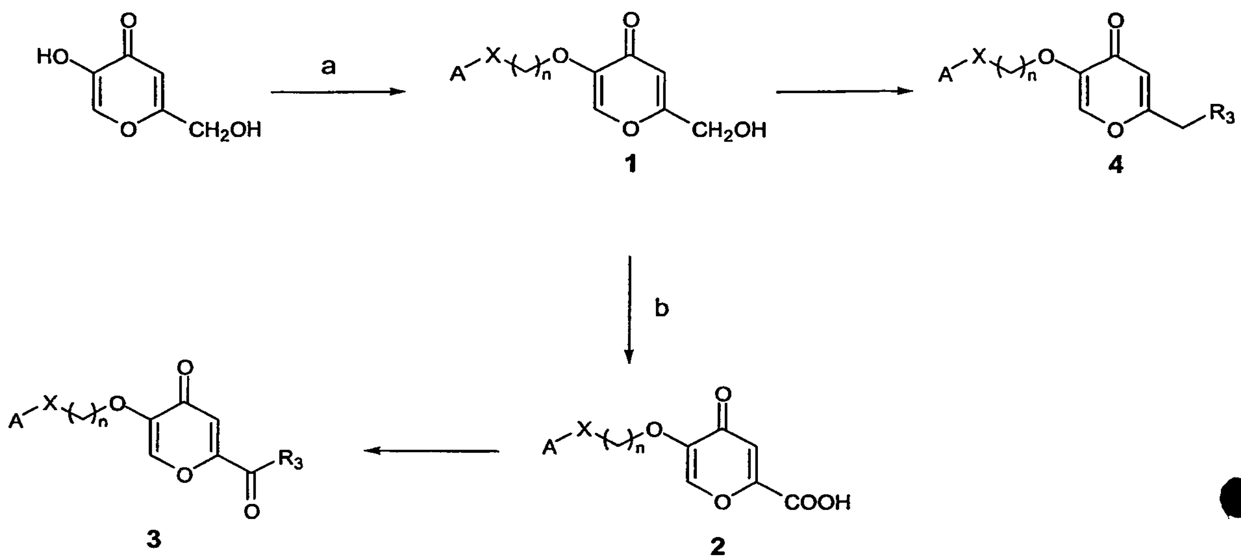
5-[3-Indol-1-yl-methyl-benzyloxy)-2-tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 8589)

5-[4-Indol-1-yl-methyl-benzyloxy)-2-tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 3986)

5-(2-Indol-1-ylmethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 4336).

The compounds according to the present invention may be prepared by various methods known to those skilled in the art. More preferably, the chemical routes identified below have been carried out. The first one (Scheme 1) includes an alkylation of kojic acid with the corresponding alkylbromide, which gives rise to the desired 2-(hydroxymethyl)-4*H*-pyran-4-ones **1**. These compounds may be then oxidized, typically with chromium trioxide in sulfuric acid, to produce the acid derivatives **2**, which can be readily converted into the corresponding analogues of general structure **3**. Additionally, the hydroxymethyl derivatives **1** provide the compounds **4** by standard procedures.

Scheme 1



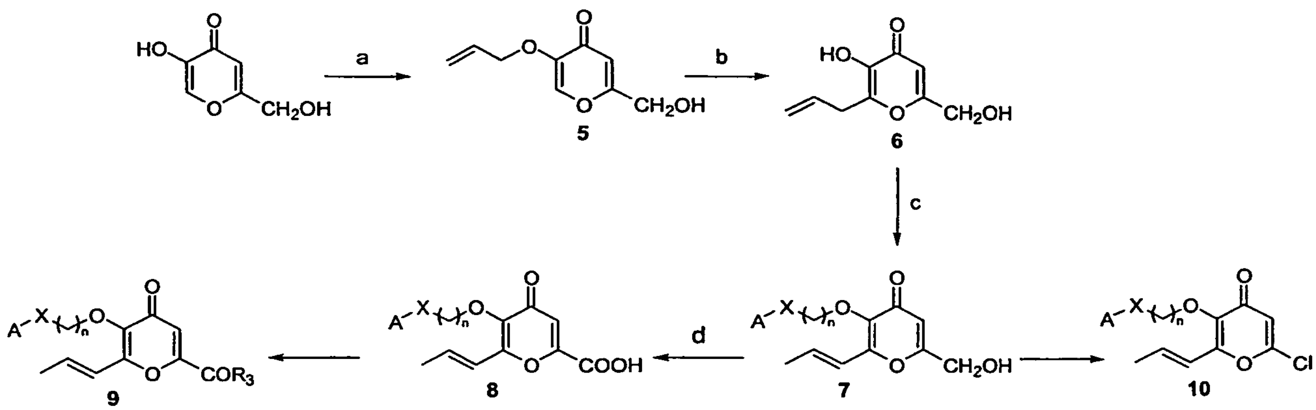
Reagents and conditions: a) K_2CO_3, Br-$(CH_2)_n$X-A, DMF, 50°C; b) Jones reagent, 50°C to rt, acetone;

Step a) of this method is more preferably conducted in a solvent, such as DMF, at a temperature comprised between 40 and 70°C, typically around 50°C.

In step b), the compounds are preferably reacted in the presence of the Jones reagent and in a solvent, such as acetone, while the temperature is decreased to reach room temperature.

The second preferred chemical route (Scheme 2) corresponds to an alkylation of kojic acid with allylbromide, which gives rise the 4*H*-pyran-4-one derivative **5.** This compound is then thermally isomerised to **6**. The general protocol for the *O*-alkylation produces simultaneously not only the alkylation but also the migration of the double bond to the conjugated position affording derivatives **7.** These alcohols are oxidized with Jones reagent to provide the acids of general structure **8.** Compounds **7** and **8** are derived to give analogues **9** and **10**.

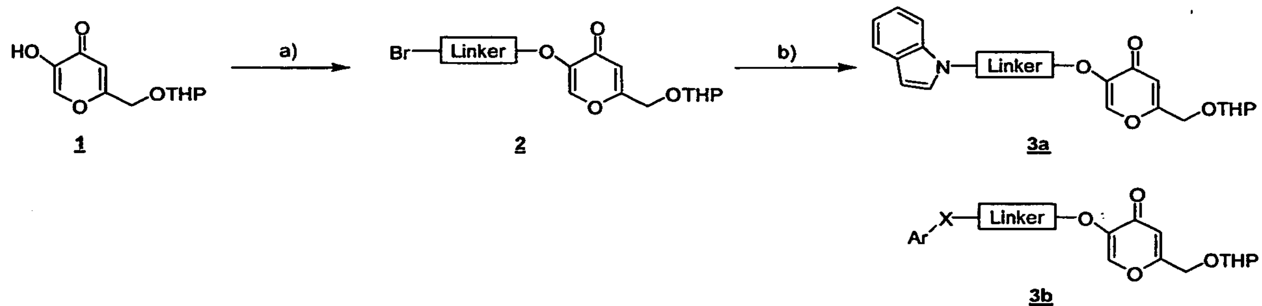
Scheme 2:



Reagents and conditions: a) Br, K_2CO_3; b)Δ ; c) K_2CO_3, Br-$(CH_2)_n$X-A; DMF, 50°C; d) Jones reagent

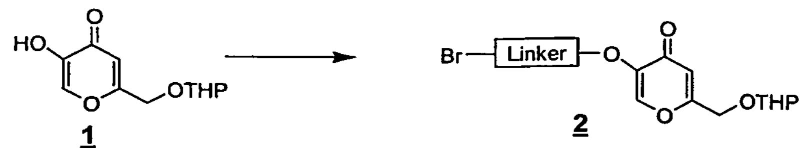
Other chemical routes can been carried out to prepare compounds of formula (I). They are more specifically described below.

In scheme 3, compounds included in the structures 3a and 3b can be obtained in two steps starting from compound 1 (described by Miyano, M.; Deason, J. R.; Nakao, A.; Stealey, M. A.; Villamil, C. I.; et al. *J. Med. Chem.* **1988**; 31, 1052-1061).



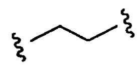
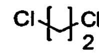
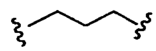
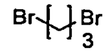
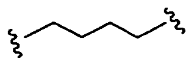
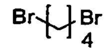
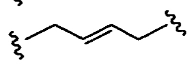
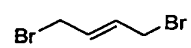
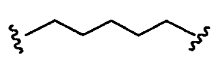
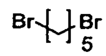
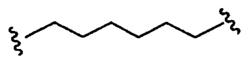
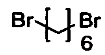
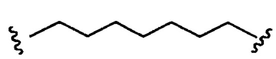
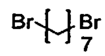
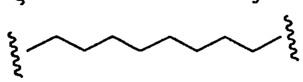
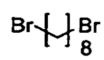
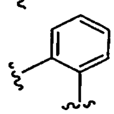
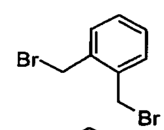
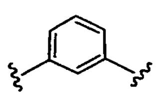
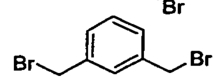
Scheme 3. a) Cs_2CO_3, DMF, dihalogenoalkane or dihalogenoarylalkane, b) Nucleophile ArXH or indole, NaH, DMSO, DMF or THF.

Table 1



1

2

#C's	Linker	Conditions	Alkylating Agent	Yield
2		Cs_2CO_3, DMF, 5°C		16%
3		Cs_2CO_3, DMF, 50°C, 2.5h		66%
4		Cs_2CO_3, DMF, 80°C, 2.5h		71%
4		Cs_2CO_3, DMF, 80°C, 2.5h		12%
5		Cs_2CO_3, DMF, 80°C, 2.5h		95%
6		Cs_2CO_3, DMF, 80°C, 2.5h		23%
7		Cs_2CO_3, DMF, 80°C, 2.5h		79%
8		Cs_2CO_3, DMF, 80°C, 2.5h		62%
4		Cs_2CO_3, DMF, 80°C, 2.5h		11%
5		Cs_2CO_3, DMF, 80°C, 2.5h		22%

Compound 1 can be treated under alkylation conditions preferably conducted in a solvent, such as DMF or THF, at a temperature between 5°C and 70°C, typically around 80°C using a base such as cesium carbonate or NaH and a dihalogenoalkane or dihalogenoarylalkane (table 1). The resulting alkylated product 2 can be substituted in a reaction (step b) involving a base such as NaH and a nucleophile such as indole but also phenol, aniline or benzenethiol derivatives (ArXH nucleophiles) as described in table 2 and table 3. The preferred solvents are DMF, THF and DMSO and the reaction is conducted at a temperature between 25°C and 100°C.

Table 2:

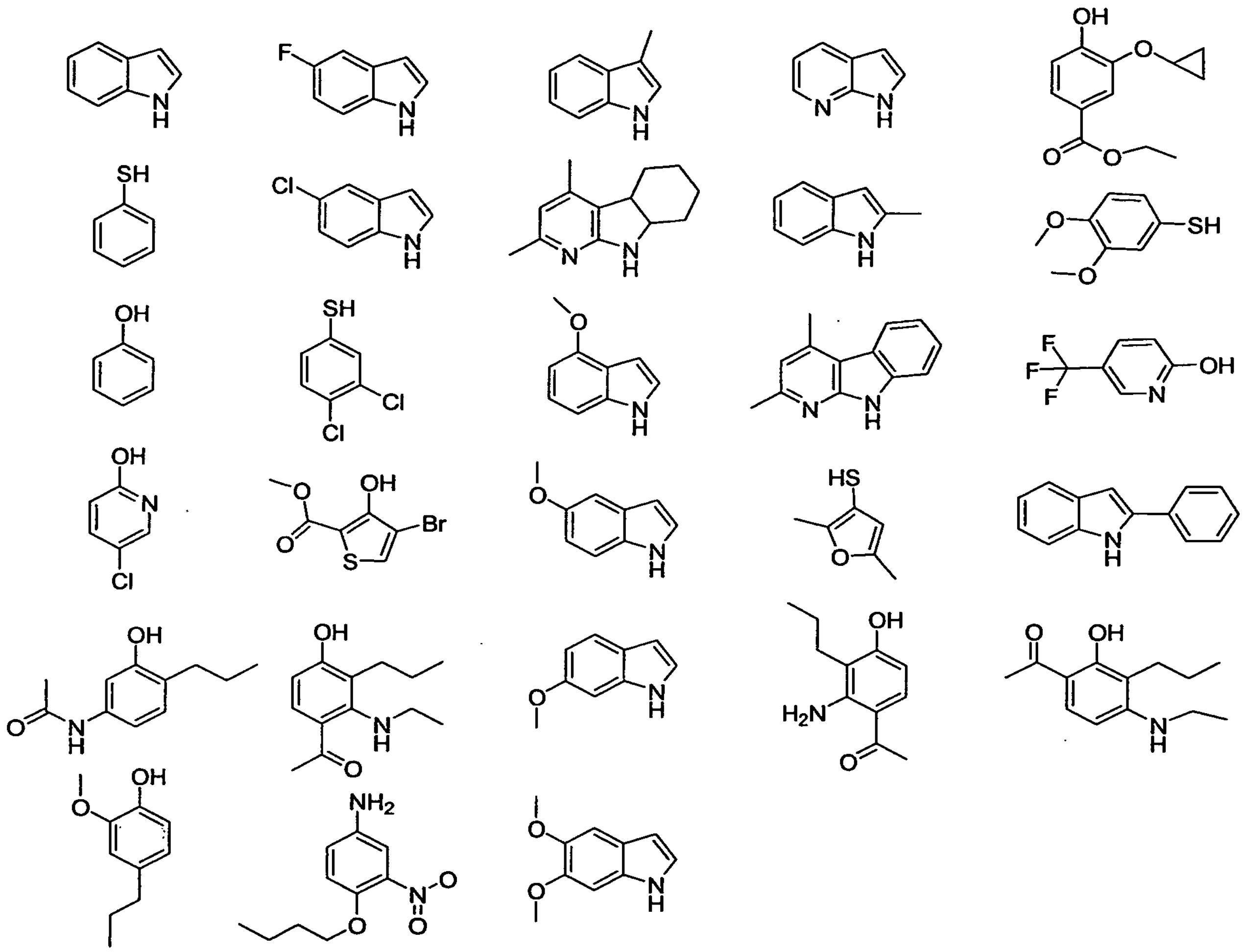
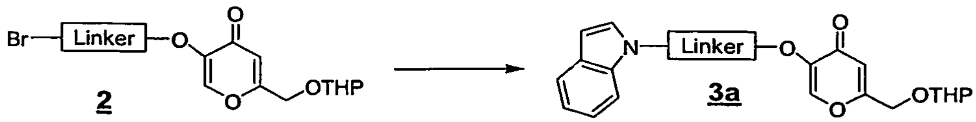
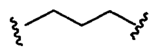
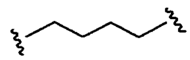
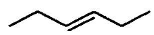
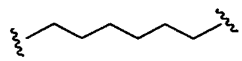
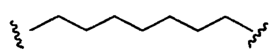
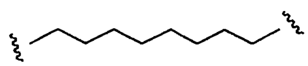
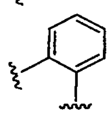
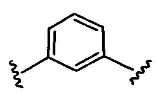
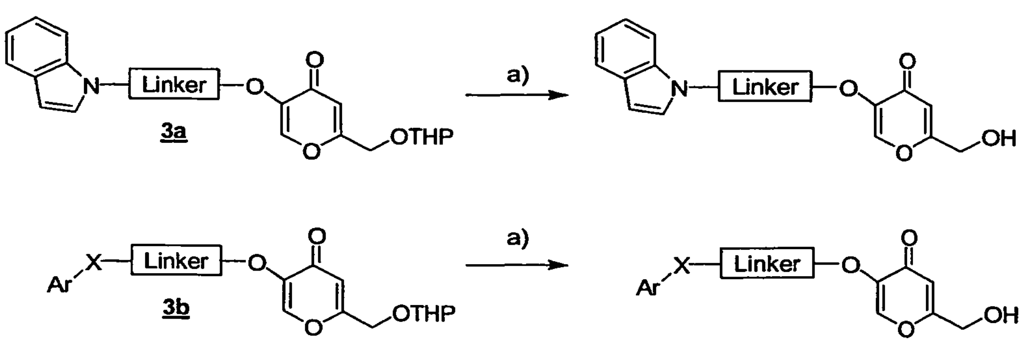


Table 3



	#C's	Linker	Conditions	Nucleophile ArXH	Yield
EHT 4283	3		NaH, DMSO 60°C	Indole	21%
EHT 5741	4		NaH, DMSO 60°C	Indole	43%
EHT 6895	4		NaH, DMSO 60°C	Indole	16%
EHT 2358	6		NaH, DMSO 60°C	Indole	15 %
EHT 8733	7		NaH, DMSO 60°C	Indole	39%
EHT 2271	8		NaH, DMSO 60°C	Indole	39%
EHT 4336	4		NaH, DMSO 60°C	Indole	21%
EHT 3986	5		NaH, DMF 25°C	Indole	50%

Scheme 4



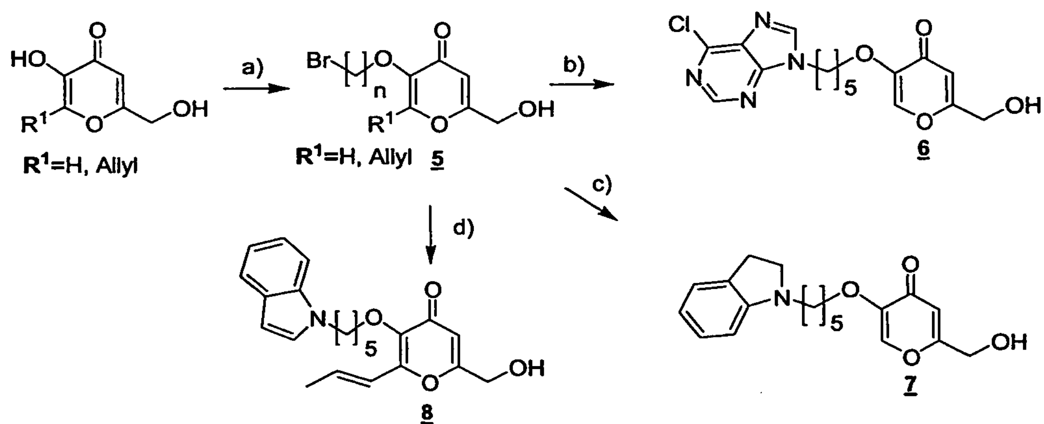
a) Dowex 50WX8-200, MeOH.

Compounds included in the generic structures **3a** and **3b** can be deprotected to their corresponding alcohol in methanol with an acid source such as Dowex resin 50WX8-200 at a temperature comprised between 5°C and 30°C, typically around 25°C (scheme 4).

Compounds **6**, **7** **and** **8** can be obtained directly in two steps from kojic acid or 2-propenyl kojic acid (scheme 5).

Intermediates **5** are more preferably obtained in a solvent, such as DMF, at a temperature comprised between 5°C and 70°C, typically around 50°C with a base such as potassium carbonate, catalytic sodium iodide and 1,5-dibromopentane. Compound **6** can be obtained in a solvent, such as DMF, at a temperature between 25°C and 100°C, typically around 70°C with a base such as triethylamine and 6-chloro-9*H*-purine. Compound **7** can be obtained in a solvent such as ethanol, at reflux with a base such as potassium carbonate and 2,3-dihydro-1*H*-indole. Compound **8** can be obtained in a solvent such as dimethylformamide, typically around 25°C with a base such as cesium carbonate, catalytic sodium iodide and 1*H*-indole.

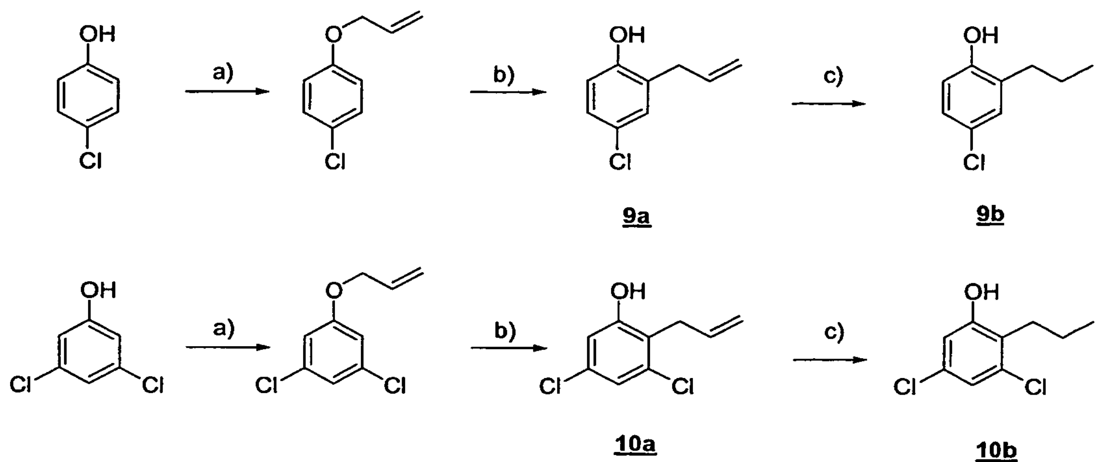
Scheme 5.



a) K_2CO_3, NaI, DMF, 50°C, dibromopentane b) Chloropurine, TEA, DMF, 70°C. c) Indoline, K_2CO_3, EtOH, reflux. d) Cs_2CO_3, DMF, NaI cat., RT.

The non-commercially available phenols **6** and **7** used for the synthesis of these new pyranone derivatives were prepared by Claisen rearrangement as described in scheme 6.

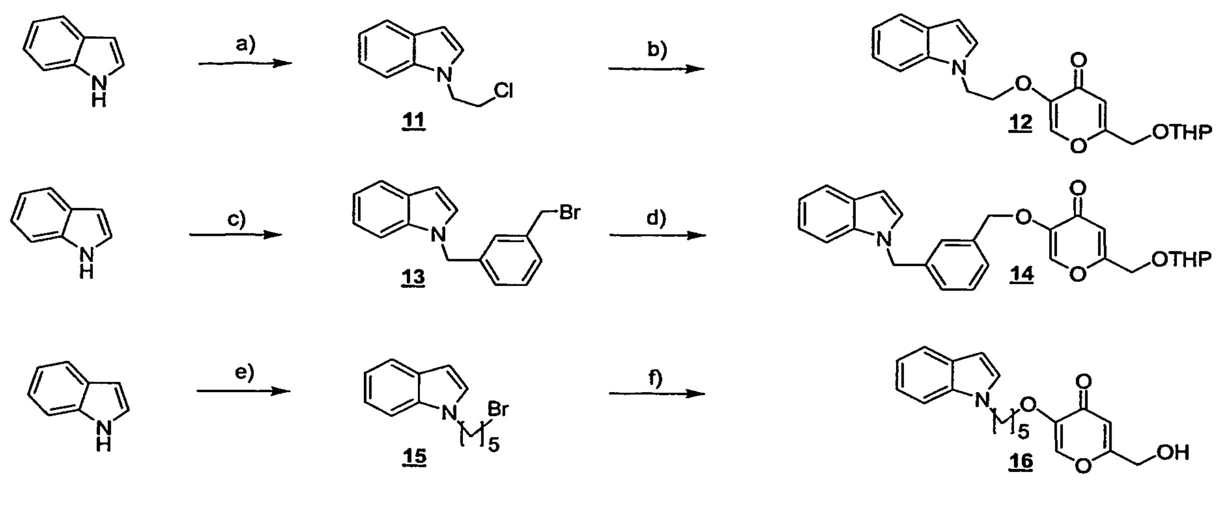
Scheme 6



a) allyl bromide, K_2CO_3, NaI, 2-butanone, reflux. b) ethylene glycol, 200°C. c) Raney-Ni H_2, 30 psi, toluene, methanol, 25°C.

The *O*-alkylation of commercially available 4-chloro and 3,4-dichlorophenol can be conducted in a solvent such as 2-butanone, at reflux with a base such as potassium carbonate in presence of catalytic sodium iodide and allyl bromide. The Claisen rearrangement can be performed in ethyleneglycol at a reflux to yield to O-allylphenols **9a** and **10a**. Phenols **9a** and **10a** can be respectively reduced to the 2-propylphenols **9b** and **10b** using hydrogen at 30 psi with Raney-Ni as a catalyst in a solvent such as methanol/toluene at 25°C (Scheme 6).

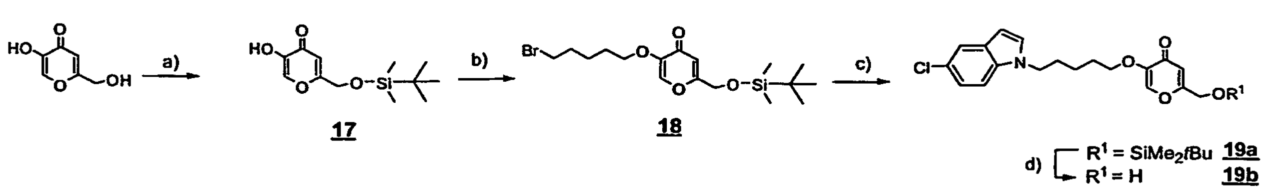
Scheme 7



a) KOH, Bu_4NF, H_2O, 1,2-dichloroethane 70-90°C. b) Cs_2CO_3, 1, DMF, NaI cat., 90°C. c) NaH, DMF, RT, 1,3-bis-bromomethylbenzene. d) NaH, 1, THF, e) KOH, 1,5-dibromopentane, DMF, 35°C. f) Cs_2CO_3, Kojic Acid, DMF, NaI cat., RT.

The alkylation of indole can be conducted with a base such as potassium hydroxide in a solvent such as H_2O in dichloroethane with a phase transfer catalyst such as tetrabutylammonium fluoride, at a temperature between 70°C and 90°C to give intermediate 11 (scheme 7). Alternatively, it can be perfomed with a base such as sodium hydride in dimethylformamide with 1,3-bis-bromomethylbenzene at 25°C to yield to intermediate 13. Moreover, indole can be alkylated with 1,5-dibromopentane using potassium hydroxide in dimethylformamide around 35°C to give intermediate 15 (Dehaen, W. and Hassner, A. *J. Org. Chem.* **1991**, *56*, 896). Subsequently, 11, 13 and 15 can be respectively alkylated with compound 1 or kojic acid using as a base cesium carbonate or sodium hydride as described in scheme 7 to yield to compounds 12, 14 and 16 (Scheme 7).

Scheme 8

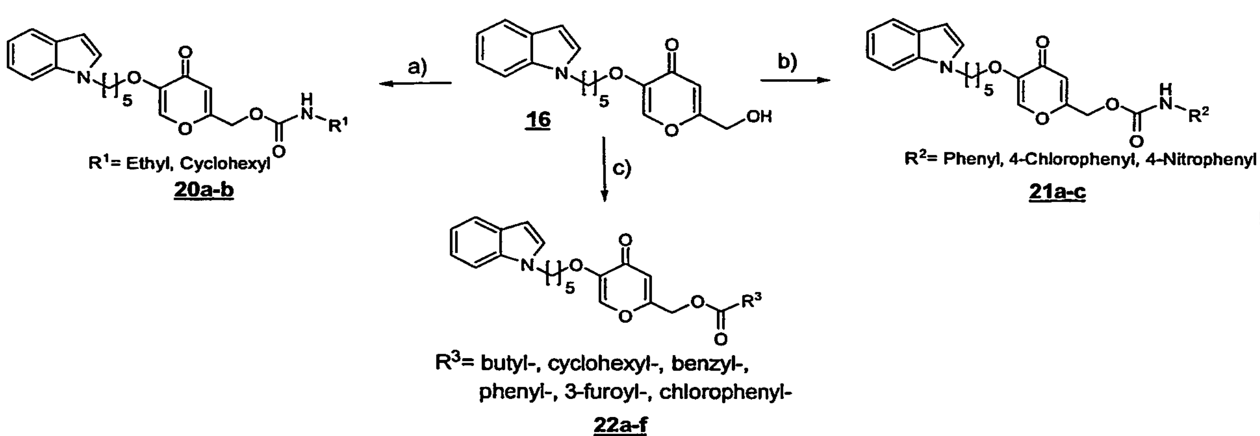


a) TBDMSCl, CH_2Cl_2, TEA, RT. b) Cs_2CO_3, DMF, dibromopentane, 50°C c) 5-Chloroindole, DMF, NaH, R.T d) TBAF, THF, RT

Intermediate **18** can be prepared from the silylated ether **17** (Sefkow, M.; Kaatz, H. *Tetrahedron Lett*, **1999,** *40,* 6561-6562) with a base such as cesium carbonate and 1,5-dibromopentane in dimethylformamide at 50°C (Scheme 8).

Derivative **19a** can be prepared from intermediate **18** using sodium hydride, 5-chloroindole in dimethylformamide at room temperature. Subsequent deprotection of silylated ether **19a** using *n*-tetrabutylammonium fluoride in tetrahydrofuran at room temperature led to alcohol **19b** (scheme 8).

Scheme 9



a) R^1-N=C=O, CuCl, DMF, 25°C b) R^2-N=C=O, THF, Et_3N, 25°C c) DCC, DMAP, CH_2Cl_2, R^3CO_2H

Carbamate derivatives **20a**, **20b** can be prepared prepared from alcohol **16** by a method that is more preferably conducted in a solvent such as DMF in presence of CuCl and respectively with ethyl- or cyclohexyl-isocyanate at a temperature comprised between 5°C and 40°C, typically around 25°C (Scheme 9).

Carbamate derivatives **21a-c** can be prepared prepared from alcohol **16** by a method that is more preferably conducted in a solvent such as THF in presence of triethylamine and respectively with phenyl, 4-chlorophenyl, 4-nitrophenyl-isocyanate at a temperature comprised between 5°C and 40°C, typically around 25°C (Scheme 9).
Ester derivatives **22a-f** can be prepared prepared from alcohol **16** by a method that is more preferably conducted in a solvent such as THF with a base such as dimethylaminopyridine, dicyclohexylcarbodiimide and respectively with pentanoic acid, cyclohexanecarboxylic acid, phenylacetic acid, furan-3 carboxylic acid, benzoic acid, and 4-chlorobenzoic acid (Scheme 9).

These methods for preparing compounds of formula (I) represent further objects of the present application.
It should be understood that other ways of producing these compounds may be designed by the skilled person, based on common general knowledge and following guidance contained in this application.
In order to prepare compounds of formula (I) wherein Y is NR_7, kojic acid can be first protected on the hydroxyl group and then be reacted with R_7NH_2 to give rise a *N*-pyridone derivative (J. Heterocyclic Chemistry, 1986, 23 : 5-8). This *N*-pyridone derivative is thereafter deprotected and may react as described above following schemes 1 and 2. Another synthesis of *N*-substituted-pyridone is described by Korenova, A et al. in J. Chem. Pap, 1997, No.6, 51, 383-389.

As indicated above, a further object of this invention relates to a pharmaceutical composition comprising at least one compound of formula (I), as defined above, and a pharmaceutically acceptable vehicle or support.

The compounds may be formulated in various forms, including solid and liquid forms, such as tablets, gel, syrup, powder, aerosol, etc.
The compositions of this invention may contain physiologically acceptable diluents, fillers, lubricants, excipients, solvents, binders, stabilizers, and the like. Diluents that may be used in the compositions include but are not limited to

dicalcium phosphate, calcium sulphate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, powdered sugar and for prolonged release tablet-hydroxy propyl methyl cellulose (HPMC). The binders that may be used in the compositions include but are not limited to starch, gelatin and fillers such as sucrose, glucose, dextrose and lactose.

Natural and synthetic gums that may be used in the compositions include but are not limited to sodium alginate, ghatti gum, carboxymethyl cellulose, methyl cellulose, polyvinyl pyrrolidone and veegum. Excipients that may be used in the compositions include but are not limited to microcrystalline cellulose, calcium sulfate, dicalcium phosphate, starch, magnesium stearate, lactose, and sucrose. Stabilizers that may be used include but are not limited to polysaccharides such as acacia, agar, alginic acid, guar gum and tragacanth, amphotsics such as gelatin and synthetic and semi-synthetic polymers such as carbomer resins, cellulose ethers and carboxymethyl chitin.

Solvents that may be used include but are not limited to Ringers solution, water, distilled water, dimethyl sulfoxide to 50% in water, propylene glycol (neat or in water), phosphate buffered saline, balanced salt solution, glycol and other conventional fluids.

The dosages and dosage regimen in which the compounds of formula (I) are administered will vary according to the dosage form, mode of administration, the condition being treated and particulars of the patient being treated. Accordingly, optimal therapeutic concentrations will be best determined at the time and place through routine experimentation.

The compounds according to the invention can also be used enterally. Orally, the compounds according to the invention are suitable administered at the rate of 100 µg to 100 mg per day per kg of body weight. The required dose can be administered in one or more portions. For oral administration, suitable forms are, for example, tablets, gel, aerosols, pills, dragees, syrups, suspensions, emulsions, solutions, powders and granules; a preferred method of

administration consists in using a suitable form containing from 1 mg to about 500 mg of active substance.

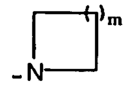
The compounds according to the invention can also be administered parenterally in the form of solutions or suspensions for intravenous or intramuscular perfusions or injections. In that case, the compounds according to the invention are generally administered at the rate of about 10 µg to 10 mg per day per kg of body weight; a preferred method of administration consists of using solutions or suspensions containing approximately from 0.01 mg to 1 mg of active substance per ml.

The compounds of formula (I) can be used in a substantially similar manner to other known anti-tumor agents for treating (both chemopreventively and therapeutically) various tumors. For the compounds of this invention, the anti-tumor dose to be administered, whether a single dose, multiple dose, or a daily dose, will of course vary with the particular compound employed because of the varying potency of the compound, the chosen route of administration, the size of the recipient, the type of tumor, and the nature of the patient's condition. The dosage to be administered is not subject to definite bounds, but it will usually be an effective amount, or the equivalent on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active drug to achieve its desired pharmacological and physiological effects. An oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, appropriate protocols for the effective administration of the compounds of this present invention, such as by referring to the earlier published studies on compounds found to have anti-tumor properties.

According to another aspect, the present invention relates to a use of an effective amount of at least one compound of formula (I) as defined above for the preparation of a pharmaceutical composition for the treatment of a disease associated with abnormal cell proliferation, wherein :

R_1 is CH_2R_3 or COR_3;

R_2 represents a hydrogen atom or an alkenyl group containing from 3 to 6 carbon atoms;

R_3 is -OH, $-OR_4$, $-SR_4$, $-NR_5R_6$, or  ;

R_4 represents a group selected from alkyl containing from 1 to 6 carbon atoms, a cycloalkyl group a radical $-CONR_5R_6$, aryl, a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero- atoms selected from oxygen, sulfur and nitrogen, heteroaryl, aralkyl, heteroaralkyl, alkanoyl or cycloalkanoyl from 2 to 6 carbon atoms, arylcarbonyl, heteroarylcarbonyl, arylalkanoyl and heteroarylalkanoyl ;

R_5 and R_6, independently from each other, are selected from a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

m is 2 or 3 ;

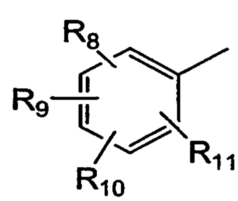
"linker" represents $(CH_2)_n$, wherein n represents an integer between 1 and 10 inclusive or a xylenyl group;

Y represents an oxygen atom, a sulfur atom or a radical $-NR_7-$;

R_7, identical or different, is selected from a group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

- either :

X represents an oxygen atom, a sulfur atom or a radical $-NR_7-$;
A represents either a substituted phenyl group of formula



in which:

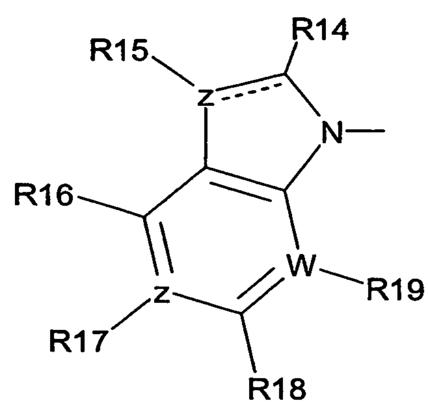
R_8, R_9, R_{10} and R_{11}, independently from each other, are selected from a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an alkenyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, a (C_1-C_{10})alkoxycarbonyl group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, a -NHCO(C_1-C_6)alkyl group, $-NO_2$, -CN, a $-NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group; preferably R_8, R_9, R_{10} and R_{11}, not being simultaneously hydrogen atom,

or alternatively two substituents, R_8 and R_9, may form together a mono- or poly-cyclic hydrocarbon group with the carbon atoms of the phenyl group they are attached and the two other substituents, R_{10} and R_{11}, are as defined above ;

or A represents a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero-atoms selected from oxygen, sulfur and nitrogen, said ring is bonded directly to X;

R_{12} and R_{13}, independently from each other, are selected in the group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

- or X-A represents a group of formula (II) :



wherein :

R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, independently from each other, represent a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, an aryl

group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, $-NO_2$, -CN, a $-NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group, R_{12} and R_{13} being as defined above; alternatively, R_{14} and R_{15} may form together with the bond they are attached thereto a cycloalkyl group (preferably a cyclohexyl group) or an aryl group (preferably a phenyl group);

W represents a carbon or nitrogen atom;

Z represents a carbon or nitrogen atom.

Preferred compounds for use according to the invention include any sub-group as defined above and any specific compounds as identified above.

A further object of this invention is a method for the treatment of a disease associated with abnormal cell proliferation, comprising administering to a patient in need of such treatment an effective amount of at least one compound of general formula (I) as described above.

Because of their cell proliferation inhibitory activity, the compounds of this invention are suitable for treating a variety of diseases in a variety of conditions. In this regard, “treatment” or “treating” include both therapeutic and prophylactic treatments. Accordingly, the compounds may be used at very early stages of a disease, or before early onset, or after significant progression, including metastasis. The term “treatment” or “treating” designates in particular a reduction of the burden in a patient, such as a reduction in cell proliferation rate, a destruction of diseased proliferative cells, a reduction of tumor mass or tumor size, a delaying of tumor progression, as well as a complete tumor suppression.

Typical examples of diseases associated with abnormal cell proliferation include cancers and restenosis, for instance. The compounds of this invention are particularly suited for the treatment of cancers, such as solid tumors or lymphoid tumors. Specific examples include prostate cancer, ovarian cancer, pancreas

cancer, lung cancer, breast cancer, liver cancer, head and neck cancer, colon cancer, bladder cancer, non-Hodgkin 's lymphoma cancer and melanoma.

The compounds may be administered according to various routes, typically by injection, such as local or systemic injection(s). Intratumoral injections are preferred for treating existing cancers. However, other administration routes may be used as well, such as intramuscular, intravenous, intradermic, subcutaneous, etc. Furthermore, repeated injections may be performed, if needed, although it is believed that limited injections will be needed in view of the efficacy of the compounds.

A further object of this invention is a method for reducing cancer cell proliferation by administering in a subject having cancer an effective amount of compound of formula (I) as defined above.

A further object of this invention is a method for treating metastatic cancers by administering in a subject in need of such treatment an effective amount of compound of formula (I) as defined above.

A further object of this invention is the use of a compound as defined above for the preparation of a pharmaceutical composition for treating metastatic cancers or for reducing cancer cell proliferation.

Further aspects and advantages of this invention will be disclosed in the following examples, which should be regarded as illustrative and not limiting the scope of this application.

LEGEND TO THE FIGURES

Figure 1: Number of neoR NIH3T3 colonies after transfection with a vector expressing an activated Ras (RasVal12) as compared to an empty vector, in the presence or not of compound EH22900.

Figure 2: Cell survival of HCT116 cells treated with compound EH22900 in adherent and non-adherent culture conditions.

Figure 3: Staining of NIH3T3 fibroblasts with FITC-coupled phalloidin which specifically binds to actin filaments, in the presence or not of compound EH22900.

Figure 4: Percentage of invading MDA-MB-231 cells treated with 1% DMSO or different concentrations of compound EH22900 as measured in a Boyden chamber

Figure 5: Percentage of migrating MDA-MB-231 cells treated with 1% DMSO or different concentrations of compound EH22900 as measured in a Boyden chamber.

Figure 6: Examples of dose-response curves for soft agar assays. Example of a cytostatic compound (L651582, left) and of a compound EHT 8617, right).

Figure 7: Antiproliferative effect of compounds on HCT116 (top) and MDA-MB-231 (bottom) cell lines measured by MTT viability assay. 2.5 10^3 (HCT116) or 7.5 10^3 (MDA-MB-231) cells were seeded in 48-well plates in growth medium containing 10% FBS, with or without various concentrations of test compounds. Cell cultures were fed every 3 days with the appropriate media. Cell viability was determined on day 6. Data were analyzed and IC_{50}s were calculated from the dose-response curves using GraphPad Prism. Results displayed on the graph are mean $\pm$ SEM of 1 to 3 experiments.

Figure 8: Effect of the treatment of HCT116 cells with the compounds on the size of the clones grown in soft agar. 5 10^3 cells were seeded in 24-well plates in 0.3% agar-containing medium supplemented with the designated amount of compounds. After 7 days of incubation at 37°C, pictures were taken of each well

and were analyzed using the ImageJ image analysis software. In particular, clone size and number were calculated. The data were analyzed using GraphPad Prism, and IC50 was calculated. Results displayed on the graph are mean ± SEM of 2 to 3 experiments.

Figure 9: Dose response curves for clone size and clone number parameters of anchorage-independent growth assay.

Figure 10: Migration of MDA-MB-231 cells in the presence of various concentrations of L651582, and EHT 0823. 5 10^4 MDA-MB-231 cells, resuspended in culture medium with or without Fetal Bovine Serum (FBS), were seeded in the upper Boyden blind well on top of 8 µm pore-sized filters. The ability of cells to migrate through the filter was assayed in the absence or presence of FBS in the lower Boyden well. After incubation at 37°C for 16 hours, the medium was removed and replaced with calcein containing medium. After labelling, cells were washed and resuspended in HBSS and fluorescence was read in a fluoroskan. Fluorescence values were normalized against the fluorescence obtained for the 1% DMSO control. The data plotted are the means ± SEM for 2 wells under the different conditions.

Figure 11: Comparison of IC_{50} measured by MTT for various indolyl compounds bearing an $-CH_2O$-THP (THP: Tetrahydropyran group) on the kojic acid moiety with variations around the linker moiety in H460 and MDA-MB-231 cells. 2.5 10^3 (H460) to 7.5 10^3 (MDA-MB-231) cells were seeded in 48-well plates in medium containing 10% FBS and various concentrations of compounds and fed every 3 days. The number of viable cells was determined on day 6 by MTT. IC_{50}s were then calculated from dose-response curves using the bioanalysis software GraphPad Prism. Values represent the mean of 1-2 experiments performed in duplicate.

Figure 12: Comparison of IC_{50} measured by MTT for various indolyl compounds with a 5 carbons linker carrying various groups at position 6 on the kojic acid moiety.

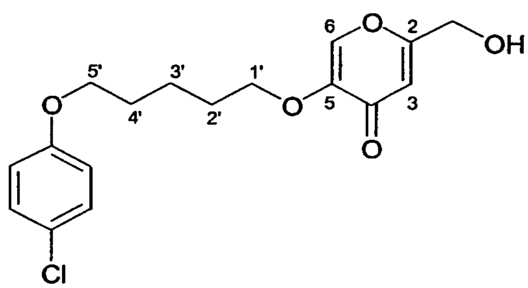
EXAMPLES

Examples 1 to 30 disclose the synthesis and physico-chemical properties of compounds according to this invention.

Examples 31 and 32 disclose the biological activity of the compounds.

Example 1: 5-[5-(4-Chlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH15500).

The compound was prepared according to Scheme 1. The structure of compound ex 1 is presented below:



Yield: 75 %; solid, mp: 95-97 °C (EtOAc / Hexane).
R_f: 0.2 (EtOAc).
IR (KBr, cm^{-1}): 3265, 3088, 2951, 1641, 1610, 1589, 1491, 1263, 1238, 1227.
^{1}H-NMR ($CDCl_3$, δ): 1.50-1.68 (m, 2H, $2H_{3'}$), 1.72-1.85 (m, 4H, $2H_{2'}$, $2H_{4'}$), 3.35 (t, J = 6.1 Hz, 1H, OH), 3.80 (t, J = 6.4 Hz, 2H, $2H_{1'}$ or $2H_{5'}$), 3.87 (t, J = 6.4 Hz, 2H, $2H_{5'}$ or $2H_{1'}$), 4.41 (d, J = 6.1 Hz, 2H, CH_2OH), 6.44 (s, 1H, H_3), 6.73 (d, J = 9.0 Hz, 2H, H_2, H_6 Ar-H), 7.15 (d, J = 9.0 Hz, 2H, H_3, H_5 Ar-H), 7.49 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.3, 28.6, 28.7, 60.7, 67.8, 69.4, 111.8, 115.6, 127.1, 129.1, 139.2, 147.7, 157.4, 166.8, 174.6.

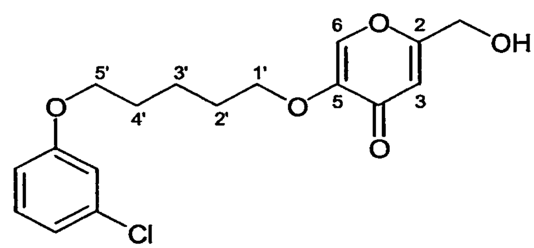
Elemental analysis for $C_{17}H_{19}O_5Cl$

Calculated: C, 60.23 %; H, 5.61 %.

Found: C, 60.28 %; H, 5.91 %.

Example 2 : 5-[5-(3-Chlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH10600).

The compound was prepared according to Scheme 1. The structure of compound ex 2 is presented below:



Yield: 71 %; solid, mp: 87-88 °C (EtOAc / Hexane).

R_f: 0.2 (EtOAc).

IR (KBr, cm^{-1}): 3248, 3082, 3060, 2955, 2906, 2874, 1645, 1608, 1589, 1573, 1479, 1452, 1278.

^{1}H-NMR ($CDCl_3$, δ): 1.45-1.61 (m, 2H, $2H_{3'}$), 1.69-1.87 (m, 4H, $2H_{2'}$, $2H_{4'}$), 3.79 (t, J = 6.3 Hz, 2H, $2H_{1'}$ or $2H_{5'}$), 3.87 (t, J = 6.3 Hz, 2H, $2H_{5'}$ or $2H_{1'}$), 3.99 (t, J = 6.4 Hz, 1H, OH), 4.41 (d, J = 6.4 Hz, 2H, CH_2OH), 6.45 (s, 1H, H_3), 6.71 (dd, J = 2.4, 0.8 Hz, 1H, H_2 Ar-H), 6.83 (m, 2H, H_4, H_6 Ar-H), 7.11 (t, J = 8.1 Hz, 1H, H_5 Ar-H), 7.55 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.6, 28.8, 28.9, 60.9, 67.9, 69.6, 111.9, 113.1, 115.1, 120.8, 130.3, 134.9, 139.5, 147.9, 159.8, 167.6, 175.1.

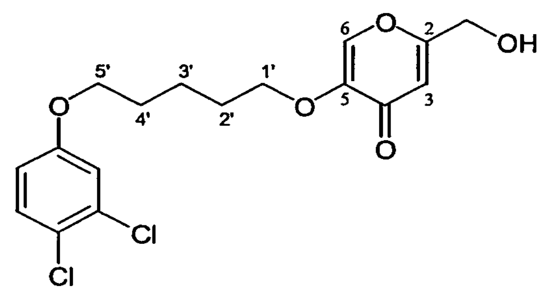
Elemental analysis for $C_{17}H_{19}O_5Cl$

Calculated: C, 60.23 %; H, 5.61 %.

Found: C, 60.20 %; H, 5.59 %.

Example 3 : 5-[5-(3,4-Dichlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH5500).

The compound was prepared according to Scheme 1. The structure of compound ex 3 is presented below:



Yield: 73 %; solid, mp: 97-99 °C (EtOAc / Hexane).

R_f: 0.2 (EtOAc).

IR (KBr, cm^{-1}): 3377, 3115, 3055, 2952, 2873, 1645, 1606, 1469, 1375, 1230, 1122, 1053, 918, 856.

^{1}H-NMR ($CDCl_3$, δ): 1.51-1.65 (m, 2H, $2H_{3'}$), 1.76-1.86 (m, 4H, $2H_{2'}$, $2H_{4'}$), 3.40 (t, *J* = 6.6 Hz, 1H, OH), 3.82 (t, *J* = 6.3 Hz, 2H, $2H_{1'}$ or $2H_{5'}$), 3.89 (t, *J* = 6.3 Hz, 2H, $2H_{5'}$ or $2H_{1'}$), 4.44 (d, *J* = 6.4 Hz, 2H, CH_2OH), 6.49 (s, 1H, H_3), 6.70 (dd, *J* = 8.7, 3.5 Hz, 1H, H_6 Ar-H), 6.93 (d, *J* = 3.5 Hz, 1H, H_2 Ar-H), 7.26 (d, *J* = 8.7 Hz,1H, H_5 Ar-H), 7.53 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.4, 28.7, 60.6, 68.2, 69.4, 111.6, 114.4, 116.2, 123.6, 130.5, 132.7, 139.1, 147.7, 157.9, 167.7, 174.9.

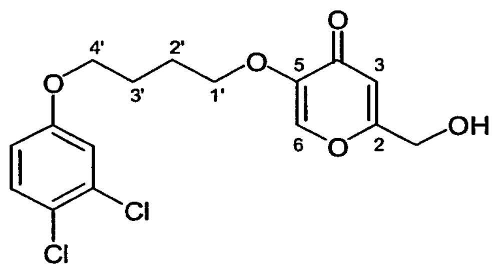
Elemental analysis for $C_{17}H_{18}O_5Cl_2$

Calculated: C, 54.71 %; H, 4.86 %.

Found: C, 54.66 %; H, 5.02 %.

Example 4 : 5-[4-(3,4-Dichlorophenyloxy)butyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH17700).

The compound was prepared according to Scheme 1. The structure of compound ex 4 is presented below:



Yield: 73 %; solid, mp: 107-108 °C (EtOAc / Hexane).

Rf: 0.2 (EtOAc).

IR (KBr, cm^{-1}): 3354, 3068, 2958, 2937, 2912, 1651, 1610, 1589, 1562, 1535, 1469, 1448, 1257, 827.

^{1}H-NMR ($CDCl_3$, δ): 1.74-1.83 (m, 4H, $2H_{2'}$, $2H_{3'}$), 3.71-3.81 (m, 5H, $2H_{1'}$, $2H_{4'}$, OH), 4.28 (d, *J* = 5.7 Hz, 2H, CH_2OH), 6.32 (s, 1H, H_3), 6.53 (dd, *J* = 8.5; 3.5 Hz, 1H, H_6 Ar-H), 6.77 (d, *J* = 3.5 Hz, 1H, H_2 Ar-H), 7.07 (d, *J* = 8.5 Hz, 1H, H_5 Ar-H), 7.37 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 25.7, 25.8, 60.9, 68.1, 69.4, 111.9, 114.6, 116.1, 123.9, 130.8, 132.8, 139.7, 147.8, 158.1, 167.7, 175.1.

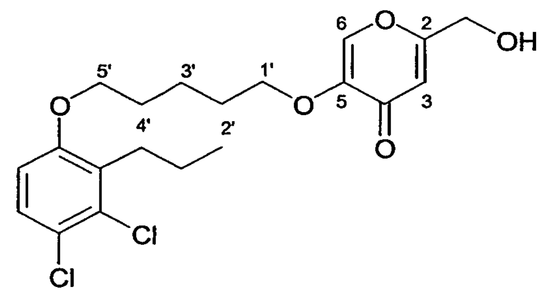
Elemental analysis for $C_{16}H_{16}O_5Cl_2$

Calculated: C, 53.48 %; H, 4.46 %.

Found: C, 53.40 %; H, 4.68 %.

<u>Example 5 : 5-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH22900)</u>.

The compound was prepared according to Scheme 1. The structure of compound ex 5 is presented below:



Yield: 73 %; solid, mp: 85 - 86 °C (EtOAc /Et_2O).

R_f: 0.2 (EtOAc).

IR (KBr, cm^{-1}): 3300, 2945, 2870, 1647, 1607, 1452, 1259, 1207, 1151, 1082, 1026, 870.

^{1}H-NMR ($CDCl_3$, δ): 0.90 (t, J = 8.3 Hz, 3H, CH_3), 1.39-1.62 (m, 4H, $2CH_2$), 1.74-1.92 (m, 4H, $2CH_2$), 2.73 (dd, J= 7.9; 5.9 Hz, 2H, CH_2), 3.13 (br s, 1H, OH), 3.81-3.93 (m, 4H, $2CH_2O$), 4.45 (s, 2H, CH_2OH), 6.52 (s, 1H, H_3), 6.63 (d, J = 8.9 Hz, 1H-Ar), 7.17 (d, J = 8.8 Hz, 1H, Ar-H), 7.72 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 14.3, 21.9, 22.7, 28.9, 29.1, 30.2, 60.9, 68.3, 69.7, 110.4, 111.9, 127.5, 131.8, 139.6, 147.9, 156.2, 175.1.

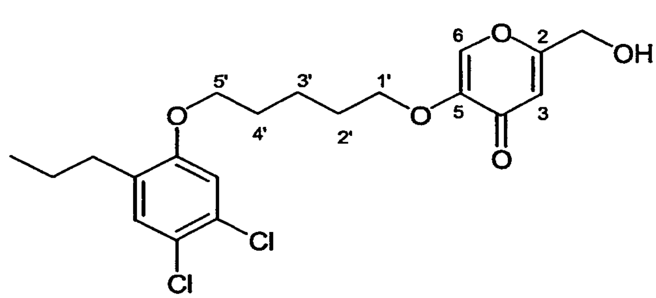
Elemental analysis for $C_{20}H_{24}O_5Cl_2$

Calculated: C, 57.83 %; H, 5.82 %.

Found: C, 57.96 %; H, 5.72 %.

Example 6 : 5-[5-(4,5-Dichloro-2-propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH30701)

The compound was prepared according to Scheme 1. The structure of compound ex 6 is presented below:



Yield: 60 %; solid, mp: 83 - 84 °C (EtOAc /Et_2O).

R$_f$: 0.2 (EtOAc).

IR (KBr, cm^{-1}): 3315, 3082, 2952, 2927, 2873, 1649, 1608, 1587, 1450, 1263, 1215, 1151, 977.

^{1}H-NMR ($CDCl_3$, δ): 0.84 (t, *J* = 7.3 Hz, 3H, CH_3), 1.39-1.62 (m, 4H, $2CH_2$), 1.72-1.98 (m, 4H, $2CH_2$), 2.47 (t, *J*= 7.8 Hz, 2H, CH_2), 3.65 (br s, 1H, OH), 3.82-3.89 (m, 4H, $2CH_2O$), 4.41 (s, 2H, CH_2OH), 6.45 (s, 1H, H_3), 6.78 (s, 1H, Ar-H), 7.08 (s, 1H, Ar-H), 7.50 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 13.8, 22.4, 22.6, 28.6, 28.7, 31.5, 60.8, 68.1, 69.5, 111.9, 113.0, 122.9, 129.5, 130.7, 131.7, 139.4, 147.4, 155.8, 167.2, 174.8.

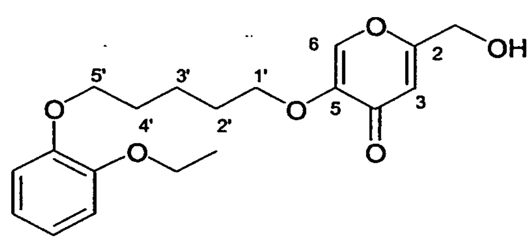
Elemental analysis for $C_{20}H_{24}O_5Cl_2$

Calculated: C, 57.83 %; H, 5.82 %.

Found: C, 58.05 %; H, 5.88 %.

<u>Example 7 : 5-[5-(2-Ethyloxyphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH18601)</u>.

The compound was prepared according to Scheme 1. The structure of compound ex 7 is presented below:



Yield: 75 %; solid, mp: 75 –76 °C (EtOAc-Et_2O).

R$_f$: 0.2 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3367, 3010, 2983, 2941, 2873, 1647, 1612, 1593, 1504, 1475, 1452, 1394,1251, 1215, 1151, 1126, 866.

^{1}H-NMR (CDCl$_3$, δ): 1.35 (t, J = 6.9 Hz, 3H, CH$_3$), 1.52-1.64 (m, 2H, CH$_2$), 1.74-1.91 (m, 4H, 2CH$_2$), 2.71 (br s, 1H, OH), 3.82 (t, J = 6.5 Hz, 2H, CH$_2$O), 3.95 (t, J = 6.5 Hz, 2H, CH$_2$O), 4.02 (q, J = 7.1 Hz, 2H, CH$_2$O), 4.41 (s, 2H, CH$_2$OH), 6.47 (s, 1H, 1H$_3$), 6.82 (s, 4H, Ar-H), 7.51 (s, 1H, 1H$_6$).

^{13}C-NMR (CDCl$_3$, δ): 14.8, 22.3, 28.6, 28.7, 60.8, 64.5, 68.8, 69.5, 111.9, 113.9, 114.1, 121.0, 121.1, 139.3, 147.7, 148.8, 166.7, 174.6.

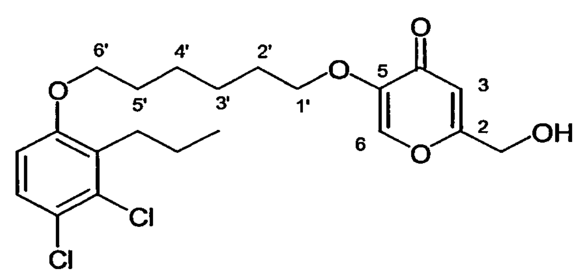
Elemental analysis for $C_{19}H_{24}O_6$

Calculated: C, 65.51 %; H, 6.89 %.

Found: C, 65.41 %; H, 7.03 %.

Example 8 : 5-[6-(3,4-Dichloro-2-propylphenyloxy)hexyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH16701).

The compound was prepared according to Scheme 1. The structure of compound ex 8 is presented below:



Yield: 75 %; solid, mp: 86 – 87 °C (EtOAc /Et$_2$O).

R$_f$: 0.3 (EtOAc).

IR (KBr, cm^{-1}): 3301, 3099, 2937, 2908, 2756, 1645, 1610, 1591, 1456, 1253, 1080, 999.

^{1}H-NMR (CDCl$_3$, δ): 0.88 (t, J = 7.4 Hz, 3H, CH$_3$), 1.37-1.56 (m, 6H, 3CH$_2$), 1.72-1.78 (m, 4H, 2CH$_2$), 2.71 (t, J = 6.4 Hz, 2H, CH$_2$-Ar), 3.04 (br s, 1H, OH), 3.79 (t, J = 6.9 Hz, 2H, CH$_2$O), 3.86 (t, J = 6.2 Hz, 2H, CH$_2$O), 4.42 (s, 2H, CH$_2$OH), 6.47 (s, 1H, H$_3$), 6.61 (d, J = 9.5 Hz, 1H, Ar-H), 7.15 (d, J = 8.6 Hz, 1H, Ar-H), 7.51 (s, 1H, H$_6$).

^{13}C-NMR ($CDCl_3$, δ): 14.1, 21.8, 25.5, 25.8, 28.9, 29.1, 30.0, 60.9, 68.2, 69.6, 110.2, 111.9, 125.1, 126.3, 127.3, 132.5, 139.3, 147.8, 156.7, 167.5, 175.2.

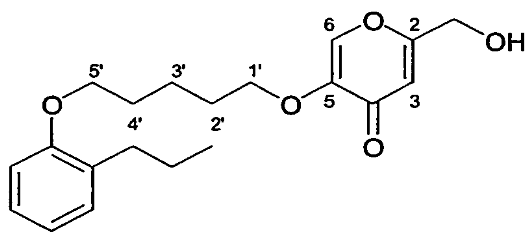
Elemental analysis for $C_{21}H_{26}Cl_2O_5$

Calculated: C, 58.75 %; H, 6.10 %.

Found: C, 58.45 %; H, 5,89 %.

Example 9 : 5-[5-(2-Propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH18900).

The compound was prepared according to scheme 1. The structure of compound ex 9 is presented below:



Yield: 73 %; oil.

***R**f*: 0.3 (EtOAc).

IR (KBr, cm^{-1}): 3350, 2954, 2933, 1649, 1612, 1492, 1452, 1242, 1209, 1151, 1126.

^{1}H-NMR ($CDCl_3$, δ): 0.85 (t, J = 6.9 Hz, 3H, CH_3), 1.45-1.95 (m, 8H, $4CH_2$), 2.50 (t, J = 7.9 Hz, 2H, CH_2), 3.25 (t, 6.5 Hz, 1H, OH), 3.80 (t, J = 7.5 Hz, 2H, CH_2O), 3.90 (t, J = 7.5 Hz, 2H, CH_2O), 4.45 (d, J = 7.7 Hz, 2H, CH_2OH), 6.45 (s, 1H, H_3), 6.65-6.85 (m, 2H-Ar), 6.95-7.10 (m, 2H-Ar), 7.45 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 14.1, 22.6, 23.0, 28.8, 29.1, 32.3, 60.8, 67.4, 69.7, 111.1, 111.8, 120.2, 126.8, 129.9, 131.2, 139.5, 147.8, 156.8, 167.5, 174.9.

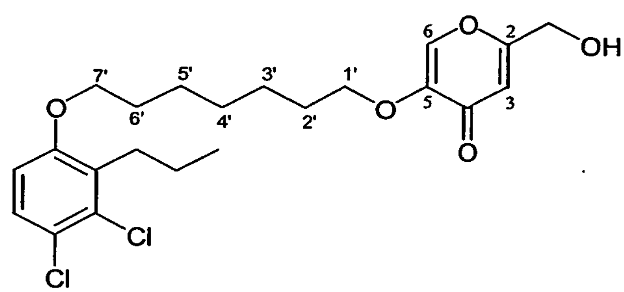
Elemental analysis for $C_{20}H_{26}O_5$

Calculated: C, 69.36 %; H, 7.51 %.

Found: C, 68.35 %; H, 7.44 %.

Example 10 : 5-[7-(3,4-Dichloro-2-propylphenyloxy)heptyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one (EH17701)

The compound was prepared according to Scheme 1. The structure of compound ex 10 is presented below:



Yield: 60%; solid, mp: 62-64 °C.

IR (KBr, cm^{-1}): 3238, 2937, 2854, 1653, 1638, 1616, 1585, 1459, 1263, 1217, 1149, 1076, 989, 949, 814.

^{1}H-NMR (CDCl$_3$, δ): 0.88 (t, *J*= 7.3 Hz, 3H, CH_3), 1.19-1.55 (m, 8H, 4CH_2), 1.69-1.81 (m, 4H, 2CH_2), 2.68-2.75 (m, 2H, CH_2), 2.98 (br s, 1H, OH), 3.77 (t, *J*= 6.2 Hz, 2H, CH_2O), 3.85 (t, *J*= 6.5 Hz, 2H, CH_2), 4.41 (s, 2H, CH_2OH), 6.41 (s, 1H, H_3), 6.59 (d, *J*= 8.9 Hz, 1H, Ar-H), 7.14 (d, *J*= 8.8 Hz, 1H, Ar-H), 7.48 (s, 1H, H_6).

^{13}C-NMR (CDCl$_3$, δ): 14.0, 21.7, 25.7, 25.8, 28.8, 28.9, 29.0, 29.9, 60.8, 68.3, 69.6, 110.2, 118.8, 127.2, 131.6, 133.0, 139.2, 147.8, 156.0, 167.0, 174.7.

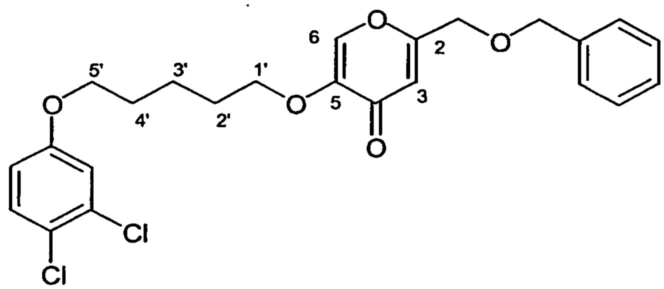
Elemental analysis for $C_{22}H_{28}O_5Cl_2$

Calculated: C, 59.60 %; H, 6.37 %.

Found: C, 59.72 %; H, 6.19 %.

Example 11 : 2-(Benzyloxymethyl)-5-[5-(3,4-dichlorophenyloxy)pentyloxy]-4*H*-pyran-4-one (EH7701).

The compound was prepared according to Scheme 1. The structure of compound ex 11 is presented below:



Yield: 52 %; solid, mp: 82 -83 °C (EtOAc-Et_2O).

***R*f**: 0.3 (EtOAc-Hexane).

IR (KBr, cm^{-1}): 3257, 3128, 3064, 2906, 1651, 1627, 1596, 1481, 1465, 1263, 999, 835, 740.

^{1}H-NMR ($CDCl_3$, δ): 1.53 (m, 2H, CH_2), 1.71 (m, 4H, $2CH_2$), 3.76-3.86 (m, 4H, $2CH_2O$), 4.21 (s, 2H, CH_2O), 4.52 (s, 2H, CH_2O), 6.41 (s, 1H, H_3), 6.65 (dd, J = 8.9, 2.9 Hz, 1H, Ar-H), 6.89 (d, J = 2.9 Hz, 1H, Ar-H), 7.17-7.34 (m, 6H, Ar-H), 7.48 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.6, 28.8, 67.7, 68.4, 69.6, 73.3, 113.6, 114.6, 116,4, 123.8, 127.9, 128.3, 128.7, 130.7, 132.8, 136.9, 139.6, 148.1, 158.2, 163.9, 174.4.

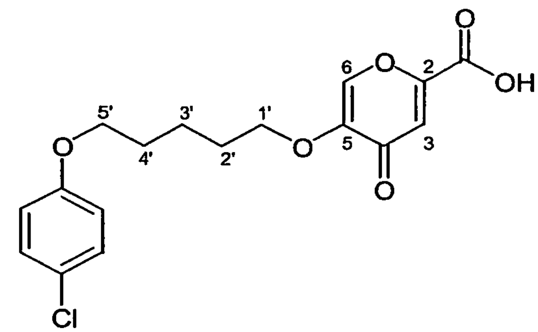
Elemental analysis for $C_{24}H_{24}Cl_2O_5$

Calculated: C, 62.14 %; H, 5.18 %.

Found: C, 61.88 %; H, 5.13 %.

<u>Example 12 : 5-[5-(4-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH17600)</u>.

The compound was prepared according to Scheme 1. The structure of compound ex 12 is presented below:



Yield: 57 %; solid, mp: 154-156 °C (MeOH).

IR (KBr, cm^{-1}): 3402, 2947, 2876, 1732, 1602, 1602, 1578, 1493, 1477, 1283, 1242, 1209.

^{1}H-NMR (DMSO-d$_6$, δ): 1.51-1.68 (m, 2H, 2H$_{3'}$), 1.75-1.88 (m, 4H, 2H$_{2'}$, 2H$_{4'}$), 3.95 (t, J = 6.3 Hz, 2H, 2H$_{1'}$ or 2H$_{5'}$), 4.05 (t, J = 6.2 Hz, 2H, 2H$_{5'}$ or 2H$_{1'}$), 6.99 (s, 1H, H$_3$), 7.03 (d, J = 8.7 Hz, 2H, H$_2$, H$_6$ Ar-H), 7.38 (d, J = 8.7 Hz, 2H, H$_3$, H$_5$ Ar-H), 8.35 (s, 1H, H$_6$).

^{13}C-NMR (DMSO-d$_6$, δ): 21.9, 28.2, 67.7, 68.5, 116.1, 116.9, 124.0, 129.1, 140.6, 148.4, 152.2, 157.9, 160.7, 173.7.

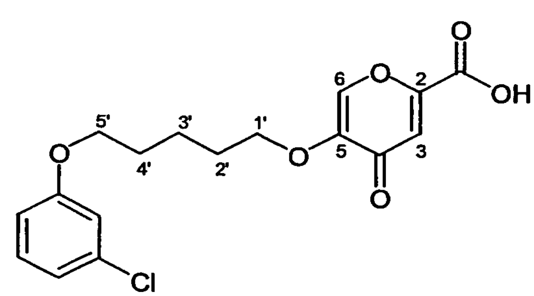
Elemental analysis for $C_{17}H_{17}O_6Cl$

Calculated: C, 57.84 %; H, 4.82 %.

Found: C, 57.61 %; H, 5.01 %.

<u>Example 13 : 5-[5-(3-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH15700)</u>.

The compound was prepared according to Scheme 1. The structure of compound ex 13 is presented below:



Yield: 60 %; solid, mp: 160-161°C (MeOH).

IR (KBr, cm^{-1}): 3439, 2941, 2912, 1733, 1635, 1601, 1576, 1284, 1232, 1209.

^{1}H-NMR (DMSO-d$_6$, δ): 1.56-1.64 (m, 2H, 2H$_{3'}$), 1.73-1.83 (m, 4H, 2H$_{2'}$, 2H$_{4'}$), 3.76 (t, J = 6.2 Hz, 2H, 2H$_{1'}$ or 2H$_{5'}$), 3.88 (t, J = 6.2 Hz, 2H, 2H$_{5'}$ or 2H$_{1'}$), 6.91-6.97 (m, 4H, H$_2$, H$_4$, H$_6$ Ar-H, H$_3$), 7.34 (t, J = 7.9 Hz, 1H, H$_5$ Ar-H), 8.31 (s, 1H, H$_6$).

^{13}C-NMR (DMSO-d$_6$, δ): 21.9, 28.1, 67.7, 68.8, 113.5, 114.3, 116.9, 120.3, 130.7, 133.6, 140.5, 148.5, 152.3, 159.5, 160.7, 172.8.

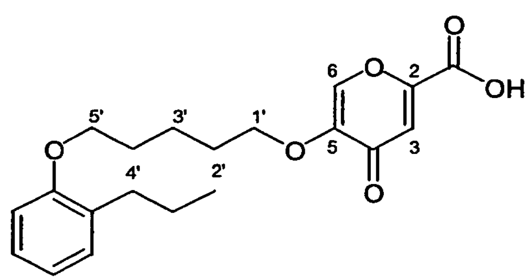
Elemental analysis for $C_{17}H_{17}O_6Cl$

Calculated: C, 57.84 %; H, 4.82 %.

Found: C, 58.05 %; H, 5.09 %.

Example 14 : 5-[5-(2-Propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH26900).

The compound was prepared according to scheme 1. The structure of compound ex 14 is presented below:



Yield: 56 %; solid, mp: 145 - 146 °C (EtOAc).

IR (KBr, cm^{-1}): 3443, 2957, 2932, 2573, 2437, 1732, 1635, 1601, 1572, 1242, 1207, 935, 760.

^{1}H-NMR (DMSO-d$_6$, δ): 0.86 (t, J = 7.4 Hz, 3H, CH$_3$), 1.00-1.21 (m, 4H, 2CH$_2$), 1.43-1.82 (m, 4H, 2CH$_2$), 2.47-2.55 (m, 2H, CH$_2$-Ar), 3.85-4.00 (m, 4H, 2CH$_2$O), 6.79-6.93 (m, 3H, H$_3$, 2H-Ar), 7.08-7.18 (m, 2H-Ar), 8.20 (s, 1H, H$_6$).

^{13}C-NMR (DMSO-d$_6$, δ): 14.0, 22.3, 22.7, 28.3, 28.6, 31.8, 67.3, 69.0, 111.5, 117.0, 120.1, 127.1, 129.7, 130.2, 140.7, 148.7, 152.8, 156.5, 161.0, 173.0.

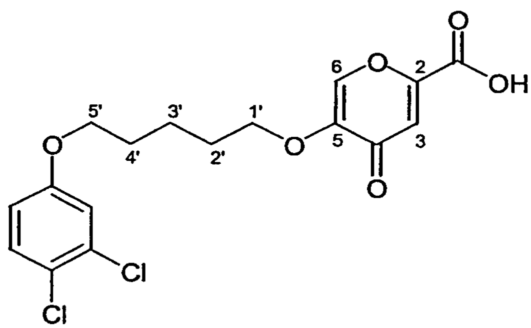
Elemental analysis for $C_{20}H_{24}O_6$

Calculated: C, 66.65 %; H, 6.71 %.

Found: C, 66.34 %; H, 6.65 %.

Example 15 : 5-[5-(3,4-Dichlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH6600).

The compound was prepared according to Scheme 1. The structure of compound ex 15 is presented below:



Yield: 55 %; solid, mp: 159-161 °C (EtOAc / Hexane)
IR (KBr, cm^{-1}): 3437, 2874, 2345, 1732, 1637, 1602, 1569, 1471, 1282, 1207.
^{1}H-NMR (DMSO-d$_6$, δ): 1.49-1.55 (m, 2H, 2H$_{3'}$), 1.68-1.77 (m, 4H, 2H$_{2'}$, 2H$_{4'}$), 3.86 (t, *J* = 6.3 Hz, 2H, 2H$_{1'}$ or 2H$_{5'}$), 3.99 (t, *J* = 6.3 Hz, 2H, 2H$_{5'}$ or 2H$_{1'}$), 6.89 (s, 1H, H$_3$), 6.94 (dd, *J* = 8.7, 3.5 Hz, 1H, H$_6$ Ar-H), 7.21 (d, *J* = 3.5 Hz, 1H, H$_2$ Ar-H), 7.48 (d, *J* = 8.7 Hz, 1H, H$_5$ Ar-H), 8.26 (s, 1H, H$_6$).
^{13}C-NMR (DMSO-d$_6$, δ): 21.7, 27.8, 68.0, 68.6, 115.3, 116.0, 116.7, 121.9, 130.7, 131.3, 140.4, 148.4, 152.2, 157.9, 160.7, 172.7.

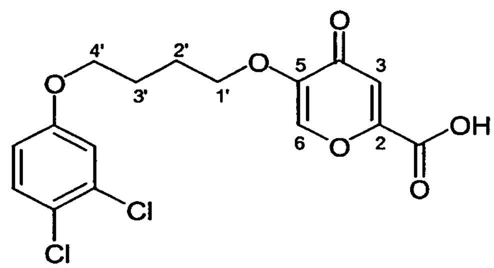
Elemental analysis for $C_{17}H_{16}O_6Cl_2$

Calculated: C, 52.73 %; H, 4.16 %.

Found: C, 52.59 %; H, 4.21 %.

Example 16 : 5-[4-(3,4-Dichlorophenyloxy)butyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH20700).

The compound was prepared according to Scheme 1. The structure of compound ex 16 is presented below:



Yield: 57 %; solid, mp: 182-183 °C (MeOH).

IR (KBr, cm^{-1}): 3452, 3107, 3076, 2972, 2918, 2875, 1735, 1618, 1598, 1562, 1475, 1249, 974, 788.

^{1}H-NMR (DMSO-d$_6$, δ): 1.55-1.75 (m, 4H, 2H$_{2'}$, 2H$_{3'}$), 3.75 (t, J = 6.2 Hz, 2H, 2H$_{1'}$ or 2H$_{4'}$), 3.88 (t, J = 6.2 Hz, 2H, 2H$_{4'}$ or 2H$_{1'}$), 6.74 (s, 1H, H$_3$), 6.79 (dd, J = 8.9, 2.9 Hz, 1H, H$_6$ Ar-H), 7.05 (d, J = 2.9 Hz, 1H, H$_2$ Ar-H), 7.33 (d, J = 8.9 Hz, 1H, H$_5$ Ar-H), 8.11 (s, 1H, H$_6$).

^{13}C-NMR (DMSO-d$_6$, δ): 25.1, 67.9, 68.7, 115.5, 116.4, 117.0, 122.3, 130.9, 131.6, 140.7, 148.6, 152.5, 158.2, 160.9, 172.9.

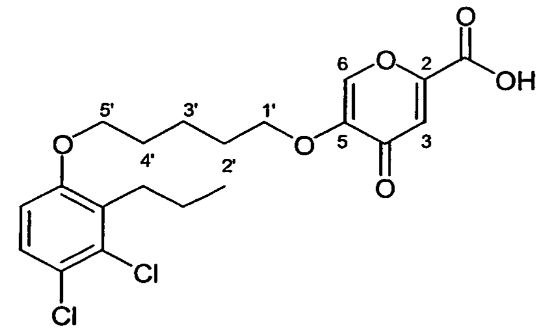
Elemental analysis for $C_{16}H_{14}O_6Cl_2$

Calculated: C, 51.47 %; H, 3.75 %.

Found: C, 51.23 %; H, 3.87 %.

Example 17 : 5-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH27900).

The compound was prepared according to Scheme 1. The structure of compound ex 17 is presented below:



Yield: 55 %; solid, mp: 155 - 156 °C (MeOH-Acetone).

IR (KBr, cm^{-1}): 3448, 3090, 2958, 2870, 2570, 2447, 1736, 1635, 1603, 1577, 1452, 1263, 1246, 1032, 935, 758.

^{1}H-NMR (DMSO-d$_6$, δ): 0.90 (t, J = 7.3 Hz, 3H, CH_3), 1.38-1.62 (m, 4H, $2CH_2$), 1.81-1.95 (m, 4H, $2CH_2$), 2.73 (t, J = 8.0 Hz, 2H, CH_2-Ar), 3.88 (t, J = 6.2 Hz, 2H, $2CH_2O$), 3.99 (t, J = 6.1 Hz, 2H, $2CH_2O$), 6.91 (s, 1H, H_3), 7.00 (d, J = 7.1 Hz, 1H, Ar-H), 7.41 (d, J = 7.5 Hz, 1H, Ar-H), 8.28 (s, 1H, H_6).

^{13}C-NMR (DMSO-d$_6$, δ): 13.7, 21.3, 21.9, 27.9, 28.1, 29.4, 68.0, 68.7, 111.5, 116.8, 123.0, 127.8, 130.5, 131.0, 140.4, 148.5, 152.3, 155.9, 160.7, 172.7.

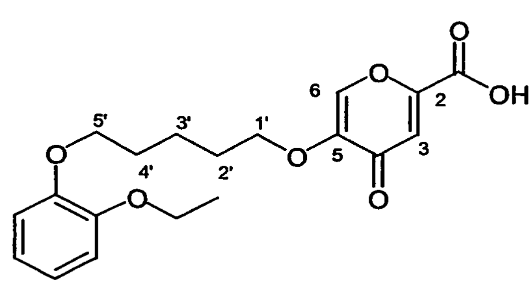
Elemental analysis for $C_{20}H_{22}O_6Cl_2$

Calculated: C, 55.96 %; H, 5.17 %.

Found: C, 56.03 %; H, 5.10 %.

<u>Example 18 : 5-[5-(2-Ethyloxyphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid (EH4701)</u>

The compound was prepared according to Scheme 1. The structure of compound ex 18 is presented below:



Yield: 75 %; solid, mp: 141–142°C.

IR ($CHCl_3$, cm^{-1}): 3068, 2875, 1732, 1637, 1602, 1575, 1253, 1211.

^{1}H-NMR (DMSO, δ): 1.47 (t, J = 6.9 Hz, 3H, CH_3), 1.71-1.78 (m, 2H, CH_2), 1.82-2.00 (m, 4H, $2CH_2$), 4.02-4.21(m, 6H, $3CH_2$), 7.00-7.15 (m, 5H, H_3, 4H, Ar-H), 8.45 (s, 1H, $1H_6$).

^{13}C-NMR (DMSO-d_6, δ): 14.5, 21.8, 27.9, 28.2, 63.6, 68.1, 68.7, 113.7, 116.6, 120.7, 140.3, 148.2, 148.3, 148.4, 152.2, 160.6, 172.2.

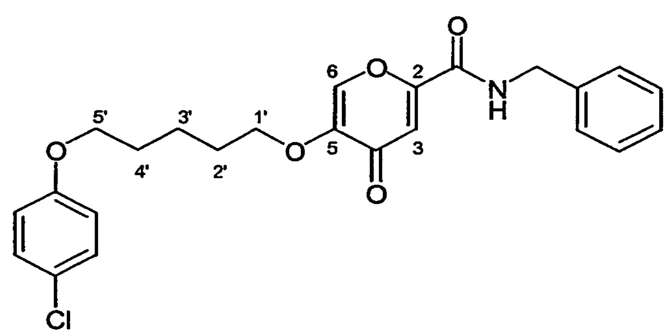
Elemental analysis for $C_{19}H_{22}O_7$

Calculated: C, 62.97 %; H, 6.12 %.

Found: C, 62.75 %; H, 6.05 %.

Example 19 : *N*-Benzyl-5-[5-(4-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxamide (EH28900).

The compound was prepared according to Scheme 1. The structure of compound ex 19 is presented below:



Yield: 56 %; solid, mp: 125-126 °C (MeOH / Et_2O).

R_f: 0.3 (EtOAc).

IR (KBr, cm^{-1}): 3423, 2947, 1732, 1637, 1602, 1569, 1469, 1282, 1207, 1122, 864.

^{1}H-NMR ($CDCl_3$, δ):1.35-1.95 (m, 6H, $3CH_2$), 3.75-3.95 (m, 4H, $2CH_2O$), 4.45 (d, J = 7.5 Hz, 2H, CH_2N), 6.72 (d, J = 9.0 Hz, 2H, Ar-H), 7.10-7.35 (m, 8H, H_3, 7H, Ar-H), 7.45 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.2, 26.7, 28.8, 29.6, 32.2, 62.6, 67.8, 115.6, 127.5, 128.0, 128.8, 129.2, 157.5.

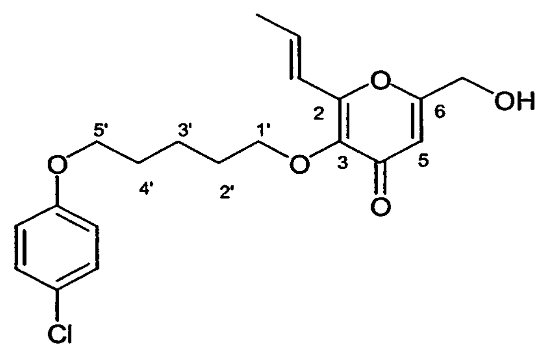
Elemental analysis for $C_{24}H_{24}ClNO_5$

Calculated: C, 65.23 %; H, 5.44 %; N, 3.17 %.

Found: C, 64.84 %; H, 5.64 %; N, 3.12 %.

Example 20 : *(E)*-3-[5-(4-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2(propen-1-yl)-4*H*-pyran-4-one (EH26101).

The compound was prepared according to Scheme 2. The structure of compound ex 20 is presented below:



Yield: 75 %; solid, mp: 84-85°C.

R$_f$: 0.3 (EtOAc / Hexane).

IR (KBr, cm^{-1}): 3350, 3012, 2943, 1718, 1654, 1641, 1596, 1560, 1492, 1473, 1436, 1286, 1244, 1217, 1197, 1170, 1153.

^{1}H-NMR ($CDCl_3$, δ): 1.48-1.79 (m, 6H, 3CH_2), 1.85 (d, *J* = 5.0 Hz, 3H, CH_3), 3.86 (t, *J* = 6.3 Hz, 2H, CH_2O), 4.00 (t, *J* = 6.3 Hz, 2H, CH_2O), 4.40 (s, 2H, CH_2OH), 6.41 (s, 1H, H_5), 6.48-6.53 (m, 2H, –CH=), 6.70 (d, *J* = 9.0 Hz, 2H, H_2, H_6 Ar-H), 7.14 (d, *J* = 9.0 Hz, 2H, H_3, H_5 Ar-H)

^{13}C-NMR ($CDCl_3$, δ): 18.7, 22.3, 28.7, 29.5, 60.6, 67.9, 72.4, 111.9, 115.6, 118.5, 125.1, 129.1, 134.5, 141.2, 154.8, 157.5, 166.1, 176.6.

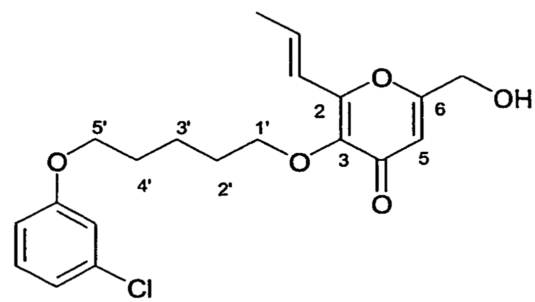
Elemental analysis for $C_{20}H_{23}ClO_5$

Calculated: C, 63.41 %; H, 6.07 %.

Found: C, 64.26 %; H, 6.03 %.

Example 21 *(E)*-3-[5-(3-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one (EH16201).

The compound was prepared according to Scheme 2. The structure of compound ex 21 presented below:



Yield: 77 %; solid, mp: 50 – 51 °C (Et_2O).

***R*_f**: 0.3 (EtOAc / Hexane).

IR ($CHCl_3$, cm^{-1}): 3392, 3018, 2943, 1654, 1643, 1595, 1469, 1436, 1284, 1215.

^{1}H-NMR ($CDCl_3$, δ): 1.45-1.81 (m, 6H, $3CH_2$), 1.85 (d, J = 5.1 Hz, 3H, CH_3), 3.88 (t, J = 6.3 Hz, 2H, CH_2O), 3.98 (t, J = 7.1 Hz, 2H, CH_2O), 4.41 (s, 2H, CH_2OH), 6.36 (s, 1H, H_5), 6.42-6.52 (m, 2H, –CH=), 6.68 (dd, J = 7.1, 1.3 Hz, 1H, Ar-H), 6.81-6.86 (m, 2H, Ar-H), 7.11 (t, J = 8.3 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 18.9, 22.4, 28.9, 29.6, 60.9, 68.0, 72.5, 112.2, 113.0, 114.8, 118.7, 120.7, 130.1, 134.5, 134.8, 141.4, 154.8, 159.8, 165.9, 176.7.

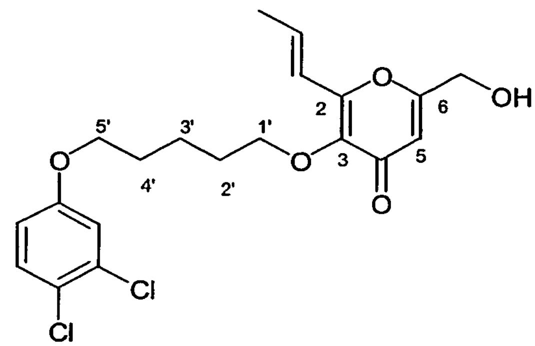
Elemental analysis for $C_{20}H_{23}ClO_5$

Calculated: C, 63.41 %; H, 6.12 %.

Found: C,62.64 %; H, 6.09 %.

Example 22 : *(E)*-(3-[5-(3,4-Dichlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one (EH30101).

The compound was prepared according to Scheme 2. The structure of compound ex 22 is presented below:



Yield: 77 %; solid, mp: 100-101°C (EtOAc/Hexane)

R_f: 0.3 (EtOAc / Hexane).

IR (KBr, cm^{-1}): 3220, 2947, 2850, 2765, 2360, 2343, 1658, 1643, 1600, 1568, 1541, 1508, 1481, 1463, 1438, 1234, 1207, 1181.

^{1}H-NMR ($CDCl_3$, δ): 1.45-1.81 (m, 6H, $3CH_2$), 1.86 (d, J = 5.0 Hz, 3H, CH_3), 2.97 (t, J = 7.0 Hz, 1H, OH), 3.85 (t, J = 7.0 Hz, 2H, CH_2O), 4.02 (t, J = 7.0 Hz, 2H, CH_2O), 4.41 (d, J = 7.0 Hz, 2H, CH_2OH), 6.35 (s, 1H, H_5), 6.49-6.55 (m, 2H, –CH=), 6.67 (dd, J = 9.0, 3.0 Hz, 1H, H_6 Ar-H), 6.91 (d, J = 3.0 Hz, 1H, H_2 Ar-H), 7.23 (d, 9.0 Hz, 1H, H_5 Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 18.6, 22.2, 28.6, 29.4, 60.6, 68.2, 72.2, 112.2, 114.3, 116.2, 118.5, 123.5, 130.4, 132.5, 134.1, 141.3, 154.4, 157.9, 164.9, 176.2.

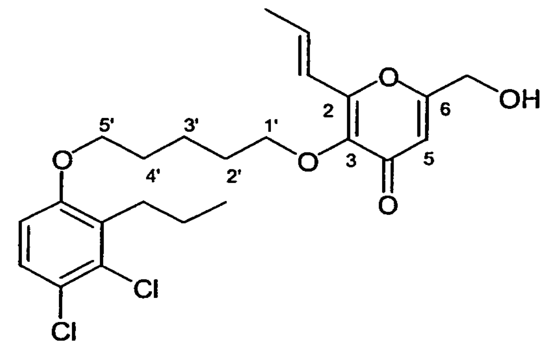
Elemental analysis for $C_{20}H_{22}O_5Cl_2$

Calculated: C, 58.12 %; H, 5.37 %.

Found: C, 58.02 %; H, 5.39 %.

Example 23 : (*E*)-3-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one (EH31101).

The compound was prepared according to Scheme 2. The structure of compound ex 23 is presented below:



Yield: 75 %; solid, mp: 75 – 76 °C (Et_2O).

R_f: 0.3 (EtOAc-Hexane).

IR (KBr, cm^{-1}): 3222, 2929, 1660, 1598, 1456, 1442, 1261, 1234, 1097, 1058, 962.

^{1}H-NMR ($CDCl_3$, δ): 0.88 (t, J = 7.3 Hz, 3H, CH_3), 1.41-1.86 (m, 8H, $4CH_2$), 1.86 (d, J = 5.1 Hz, 3H, CH_3), 2.72 (m, 3H, OH, CH_2-Ar), 3.88 (t, J = 6.2 Hz, 2H, CH_2O), 4.01 (t, J = 6.4 Hz, 2H, CH_2O), 4.42 (d, J = 4.7 Hz, 2H, CH_2OH), 6.34 (s, 1H, $1H_5$), 6.51 (m, 2H, –CH=), 6.62 (d, J = 8.8 Hz, 1H, Ar-H), 7.15 (d, J = 8.8 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 14.1, 18.8, 21.8, 22.4, 28.9, 29.6, 30.0, 61.0, 68.3, 72.4, 110.2, 112.4, 118.7, 124.1, 127.2, 131.7, 132.7, 134.1, 142.5, 154.5, 156.1, 164.8, 176.2.

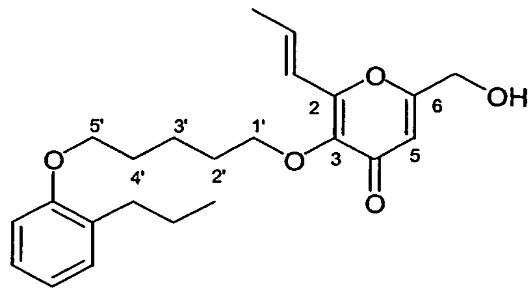
Elemental analysis for $C_{23}H_{28}O_5Cl_2$

Calculated: C, 60.66 %; H, 6.20 %.

Found: C, 60.44 %; H, 6.24 %.

Example 24 : *(E)*-6-(Hydroxymethyl)-2-(propen-1-yl)-3-[5-(2-propylphenyloxy)pentyloxy]-4*H*-pyran-4-one (EH9301).

The compound was prepared according to Scheme 2. The structure of compound ex 24 is presented below:



Yield: 75 %; solid, mp: 67 - 68 °C (EtOAc-Et_2O).

R_f: 0.3 (EtOAc / Hexane).

IR ($CHCl_3$, cm^{-1}): 3367, 2954, 2868, 1654, 1641, 1601, 1452, 1240, 1191, 968.

^{1}H-NMR ($CDCl_3$, δ): 1.01 (t, J = 7.4 Hz, 3H, CH_3), 1.51-1.70 (m, 4H, $2CH_2$), 1.75-1.90 (m, 4H, $2CH_2$), 1.90 (d, J = 5.7 Hz, 3H, CH_3), 2.66 (t, J = 7.8 Hz, 2H, CH_2-Ar), 3.96 (t, J = 7.5 Hz, 2H, CH_2O), 4.07 (t, J = 7.7 Hz, 2H, CH_2O), 4.56 (s, 2H, CH_2OH), 6.42 (s, 1H, H_5), 6.47-6.58 (m, 2H, –CH=), 6.85-6.97 (m, 2H, Ar-H), 7.15-7.25 (m, 2H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 14.1, 18.9, 22.6, 23.1, 29.2, 29.7, 32.4, 60.9, 67.6, 72.8, 111.1, 112.1, 118.7, 120.2, 126.8, 129.9, 131.2, 134.8, 141.4, 155.2, 156.9, 176.3.

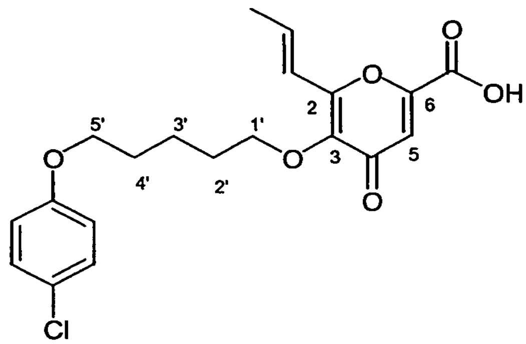
Elemental analysis for $C_{23}H_{30}O_5$

Calculated: C, 71.48 %; H, 7.82 %.

Found: C, 70.92 %; H, 7.81 %.

<u>Example 25 : (*E*)-3-[5-(4-Chlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid (EH17401)</u>.

The compound was prepared according to Scheme 2. The structure of compound ex 25 is presented below:



Yield: 55 %; solid, mp: 136 – 137 °C (EtOAc-Et_2O).

R_f: 0.3 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3076, 2943, 2914, 2871, 1732, 1647, 1629, 1596, 1581, 1541, 1492, 1442, 1286, 1244.

^{1}H-NMR ($CDCl_3$, δ): 1.48-1.60 (m, 2H, CH_2), 1.69-1.78 (m, 4H, 2CH_2), 1.87 (d, J = 6.8 Hz, 3H, CH_3), 3.83 (t, J = 6.3 Hz, 2H, CH_2O), 4.06 (t, J = 6.5 Hz, 2H, CH_2O), 6.53 (dd, J = 15.8, 1.5 Hz, 1H, –CH=), 6.75 (d, J = 9.0 Hz, 2H, Ar-H), 6.76-6.95 (m, 1H, –CH=), 7.10 (d, J = 9.0 Hz, 2H, Ar-H) 7.26 (s, 1H, H_5), 7.71 (br s, 1H, COOH).

^{13}C-NMR ($CDCl_3$, δ): 16.2, 19.1, 22.4, 28.9, 29.7, 68.1, 72.7, 115.8, 118.2, 118.5, 125.4, 129.3, 138.1, 142.9, 151.4, 156.7, 157.6, 161.1, 177.1.

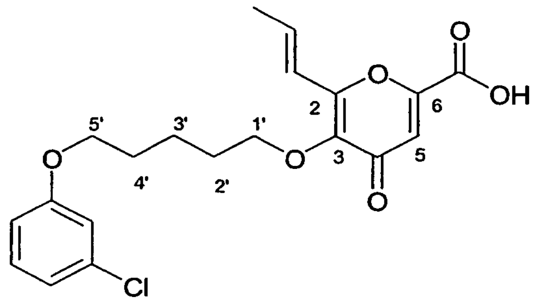
Elemental analysis for $C_{20}H_{21}O_6Cl$

Calculated: C, 61.14 %; H, 5.35 %.

Found: C, 60.93 %; H, 5.35 %.

<u>Example 26 : (*E*)-3-[5-(3-Chlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid (EH18401)</u>.

The compound was prepared according to Scheme 2. The structure of compound ex 26 is presented below:



Yield: 57 %; solid, mp: 116 – 117 °C (EtOAc-Et_2O)

R_f: 0.3 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3070, 2945, 2873, 1735, 1637, 1595, 1579, 1544, 1469, 1440, 1385, 1307, 1245, 1182.

^{1}H-NMR ($CDCl_3$, δ): 1.76-1.82 (m, 2H, CH_2), 1.88-1.96 (m, 4H, $2CH_2$), 2.09 (d, J = 5.9 Hz, 3H, CH_3), 4.07 (t, J = 6.1 Hz, 2H, CH_2O), 4.28 (t, J = 6.6 Hz, 2H, CH_2O), 6.74 (dd, J = 18.0, 1.5 Hz, 1H, –CH=), 6.92-7.08 (m, 4H, 1H, –CH=, 3H Ar-H,), 7.28 (t, J = 8.5 Hz, 1H, Ar-H), 7.47 (s, 1H, H_5), 8.12 (br s, 1H, COOH).

^{13}C-NMR ($CDCl_3$, δ): 18.9, 22.2, 28.7, 29.5, 67.8, 72.5, 112.8, 114.6, 118.0, 118.3, 120.5, 130.0, 134.6, 137.9, 142.7, 151.2, 156.5, 159.6, 160.9, 176.9.

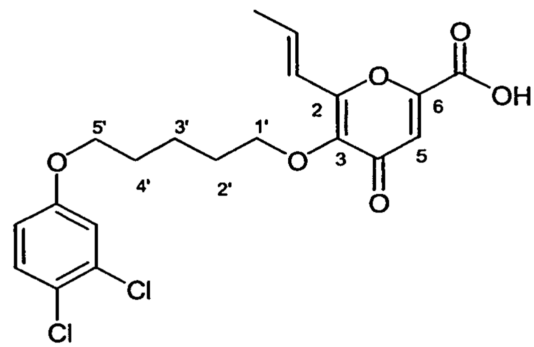
Elemental analysis for $C_{20}H_{21}O_6Cl$

Calculated: C, 61.14 %; H, 5.35 %.

Found: C, 60.57 %; H, 5.34 %.

<u>Example 27 : (*E*)-3-[5-(3,4-Dichlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid (EH10501)</u>.

The compound was prepared according to Scheme 2. The structure of compound ex 27 is presented below:



Yield: 58 %; solid, mp: 118 - 119 °C (EtOAc-Et_2O)

Rf: 0.3 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3018, 2945, 2873, 1732, 1645, 1633, 1593, 1546, 1469, 1442.

^{1}H-NMR ($CDCl_3$, δ): 1.56-1.68 (m, 2H, CH_2), 1.72-1.82 (m, 4H, $2CH_2$), 1.91 (d, J = 6.8 Hz, 3H, CH_3), 3.88 (t, J = 6.2 Hz, 2H, CH_2O), 4.09 (t, J = 7.1 Hz, 2H, CH_2O), 6.57 (dd, J = 14.9, 1.5 Hz, 1H, –CH=), 6.67 (dd, J = 8.8, 2.9 Hz, 1H, Ar-H), 6.75- 6.86 (m, 1H, –CH=), 6.91 (d, J = 2.8 Hz, 1H, Ar-H), 7.18 (d, J = 8.8 Hz, 1H, Ar-H), 7.21 (s, 1H, H_5), 7.21 (br s, 1H, COOH).

^{13}C-NMR ($CDCl_3$, δ): 19.1, 22.3, 28.7, 29.6, 68.3, 72.5, 114.5, 116.2, 118.1, 118.5, 122.9, 127.5, 130.5, 137.9, 142.9, 151.7, 156.5, 158.1, 161.1, 176.5.

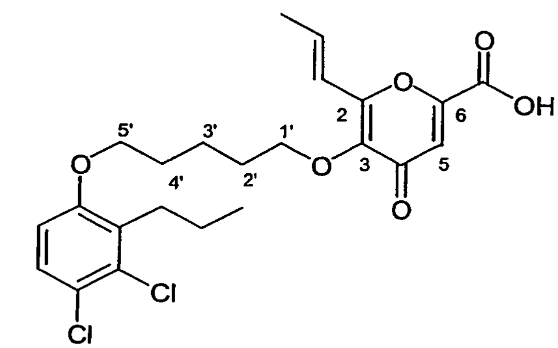
Elemental analysis for $C_{20}H_{20}Cl_2O_6$

Calculated: C, 56.22 %; H, 4.72 %.

Found: C, 55.58 %; H, 4.61 %.

Example 28 : (*E*)-3-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid (EH22501).

The compound was prepared according to Scheme 2. The structure of compound ex 28 is presented below:



Yield: 57 %; solid, mp: 161 – 162 °C (EtOAc-Et_2O).

R_f: 0.2 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3423, 3082, 2958, 2931, 1726, 1649, 1631, 1578, 1549, 1454, 1261, 1201, 1182, 968.

^{1}H-NMR (DMSO-d_6, δ): 0.72 (t, J = 7.5 Hz, 3H, CH_3), 1.23-1.43 (m, 4H, 2CH_2), 1.53-1.63 (m, 4H, 2CH_2), 1.76 (d, J = 5.2 Hz, 3H, CH_3), 2.56 (t, J = 7.4 Hz, 2H, CH_2-Ar), 3.82-3.91 (m, 4H, 2CH_2O), 6.38-6.55 (m, 2H, –CH=), 6.69 (s, 1H, H_5), 6.82 (d, J = 8.8 Hz, 1H, Ar-H), 7.26 (d, J = 8.8 Hz, 1H, Ar-H).

^{13}C-NMR (DMSO-d_6, δ): 13.8, 18.4, 21.3, 22.1, 28.2, 28.9, 29.5, 68.2, 71.7, 111.6, 117.5, 118.3, 122.7, 127.8, 130.6, 131.3, 135.5, 142.9, 151.7, 153.8, 156.1, 160.8, 174.8.

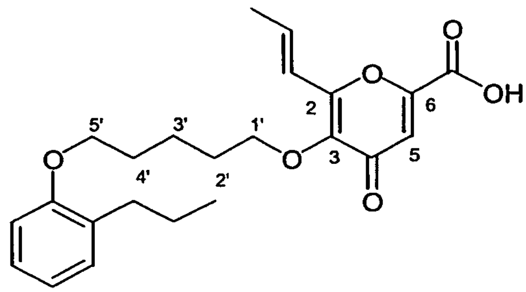
Elemental analysis for $C_{23}H_{26}Cl_2O_6$

Calculated: C, 58.86 %; H, 5.58 %.

Found: C, 58.77 %; H, 5.36 %.

Example 29 : (*E*)-2-(Propen-1-yl)-3-[5-(2-propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-6-carboxylic acid (EH15301).

The compound was prepared according to Scheme 2. The structure of compound ex 29 is presented below:



Yield: 53 %; solid, mp: 145 - 146 °C (c-Hex).

R$_f$: 0.4 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3063, 2957, 2870, 2559, 1736, 1637, 1585, 1493, 1242, 1184, 970, 908.

^{1}H-NMR ($CDCl_3$, δ): 0.78 (t, J = 7.4 Hz, 3H, CH_3), 1.40-1.51 (m, 4H, $2CH_2$), 1.65-1.76 (m, 4H, $2CH_2$), 1.83 (d, J = 6.3 Hz, 3H, CH_3), 2.44 (t, J = 7.9 Hz, 2H, CH_2-Ar), 3.84 (t, J = 5.9 Hz, 2H, CH_2O), 4.04 (t, J = 5.1 Hz, 2H, CH_2O), 6.46-6.54 (m, 1H, –CH=), 6.65-6.77 (m, 3H, 1H, –CH=, 2H, Ar-H,), 6.96-7.03 (m, 2H, Ar-H), 7.21 (s, 1H, H_5).

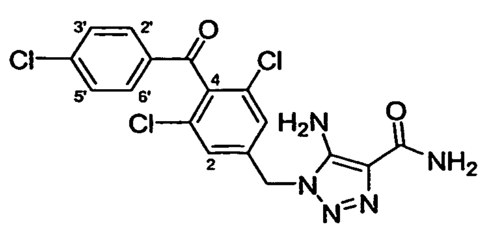
^{13}C-NMR ($CDCl_3$, δ): 14.2, 19.2, 22.7, 23.2, 29.2, 29.8, 32.5, 67.6, 72.9, 111.2, 118.3, 118.7, 120.3, 126.9, 130.0, 131.3, 138.0, 143.1, 152.0, 156.7, 157.0, 162.0, 177.1.

Elemental analysis for $C_{23}H_{28}O_6$

Calculated: C, 68.98 %; H, 7.05 %.

Found: C, 68.19 %; H, 6.97 %.

Additionally, it has been carried out the synthetic route previously reported [EP 0 304 221] that leads to the triazole L-651582:



Yield: 55 %; solid, mp: 202-204°C (MeOH).

Rf: 0.3 (EtOAc).

^{1}H-NMR (CD_3OD, δ): 5.37 (s, 2H, NH_2), 5.48 (s, 2H, CH_2–N), 5.59 (br s, 1H, NH_2), 6.78 (br s, 1H, NH_2), 7.24 (s, 2H, $H_{2,6}$), 7.42 (d, J = 8.5 Hz, 2H, $H_{3',5'}$), 7.69 (d, J = 8.5 Hz, 2H, $H_{2',6'}$).

^{13}C-NMR (CD_3OD, δ): 48.9, 128.4 (2C), 130.6 (2C), 132.1 (2C), 133.2, 135.2, 138.0, 141.0, 142.1, 146.8, 192.3.

MS (EI, 70 eV): 425 (M), 379, 353, 199, 139 (100 %), 98, 63, 55.

Elemental analysis for $C_{17}H_{12}O_2N_5Cl_3$

Calculated: C, 48.05 %; H, 2.82 %; N, 16.47 %.

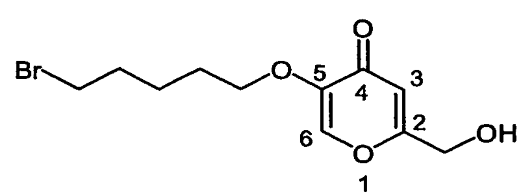
Found: C, 48.08 %; H, 3.40 %; N, 15.83 %.

Example 30 : Other compounds of formula (I)

Synthesis of intermediates 1-9

Synthesis of 5-(5-bromo-pentyloxy)-2-hydroxymethyl-4*H*-pyran-4-one (1).

A suspension containing 20 mmol of kojic acid, 40 mmol of 1,5-dibromopentane, 26 mmol of potassium carbonate and 1.8 mmol of sodium iodide in 80 mL of DMF was stirred for 24 hours at 50° C. The reaction mixture was filtered under vacuum and evaporated to dryness. The product was purified by column chromatography (hexane) to reach 1.34 g of **1** (54 % yield).



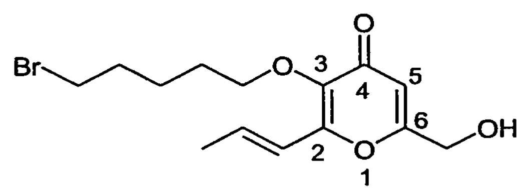
MW: 291.14; Yield: 54%.

^{1}H-NMR ($CDCl_3$, δ): 1.47-1.65 (m, 2H, CH_2), 1.75-1.98 (m, 4H, 2xCH_2), 3.23 (br s, 1H, OH), 3.36 (t, J = 6.6 Hz, 2H, CH_2Br), 3.82 (t, J = 5.7 Hz, 2H, CH_2O), 4.44 (s, 2H, CH_2OH), 6.54 (s, 1H, H_3), 7.57 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 24.5, 28.2, 32.3, 33.5, 60.8, 69.6, 111.7, 139.8, 147.6, 167.9, 174.6.

Synthesis of 3-(5-bromo-pentyloxy)-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (2).

A suspension containing 6.3 mmol of 3-hydroxy-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one (obtained in two steps from kojic acid), 12.6 mmol of 1,5-dibromopentane, 8.19 mmol of potassium carbonate and 0.59 mmol of sodium iodide in 80 mL of DMF was stirred for 24 hours at 50 °C. The reaction mixture was filtered under vacuum and evaporated to dryness. The product was purified by column chromatography (hexane) to reach 1.12 g of **2** (70 % yield).



2

MW: 331.20; Yield: 70 %.

^{1}H-NMR ($CDCl_3$, δ): 1.80-2.18 (m, 9H, CH_3 and 3xCH_2), 3.08 (br s, 1H, OH), 3.63 (t, *J* = 6.6 Hz, 2H, CH_2Br), 4.27 (t, *J* = 6.5 Hz, 2H, CH_2O), 4.73 (s, 2H, CH_2OH), 6.73-6.86 (m, 3H, 2xCH=, H_5).

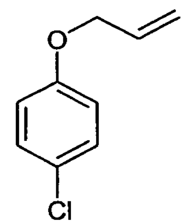
^{13}C-NMR ($CDCl_3$, δ): 19.1, 24.7, 29.3, 32.6, 33.9, 61.0, 72.6, 112.2, 118.8, 135.1, 141.5, 155.3, 166.6, 176.8.

Synthesis of 2-allyl and 2-propylphenols, 3-6.

General procedure for the O-allylation:

To a suspension of 10 mmol of 4-chlorophenol (for **3**) or 3,5-dichlorophenol (for **4**), and 13 mmol of anhydrous potassium carbonate and 0.9 mmol of sodium iodide in 45 mL of 2-butanone, 11 mmol of allyl bromide was added dropwise. The mixture was refluxed for 24 hours and after cooling it was filtered under vacuum and evaporated to dryness. The resulting crude oils were partitioned between ethyl ether and water, and the organic layers were dried over sodium sulfate, filtered and evaporated under reduced pressure.

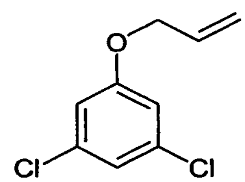
1-Allyloxy-4-chloro-benzene.



MW: 168.62; Yield: 78%.

^{1}H-NMR ($CDCl_3$, δ): 4.44 (d, *J* = 5.3 Hz, 2H, CH_2O), 5.16-5.36 (m, 2H, CH_2=), 5.84-6.03 (m, 1H, CH=), 6.74 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.13 (d, *J* = 9.1 Hz, 2H, Ar-H).

1-Allyloxy-3,5-dichloro-benzene.



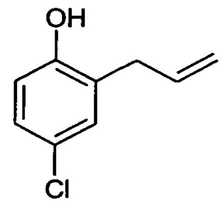
MW: 203.07; Yield: 95 %.

^{1}H-NMR ($CDCl_3$, δ): 4.53 (d, *J* = 8.2 Hz, 2H, CH_2O), 5.31-5.45 (m, 2H, CH_2=), 5.98-6.03 (m, 1H, CH=), 6.82 (s, 2H, Ar-H), 6.97 (s, 1H, Ar-H).

General procedure for the Claisen rearrangement:

Neat allyl aryl ether (10 mmol) was heated and magnetically stirred in presence of 2 mL of ethyleneglycol under an argon atmosphere at 200° C for 2 hours. After cooling the resultant mixture was washed with petroleum ether and extracted with 20 % sodium hydroxide, acidified dropwise at 0 °C with concentrated hydrochloric acid to reach pH = 1, then extracted with ethyl ether, dried over magnesium sulphate and evaporated to dryness.

2-Allyl-4-chloro-phenol (3).

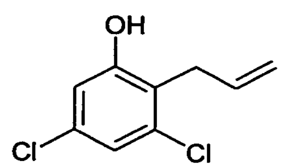


3

MW: 168.62; Yield: 47 %.

^{1}H-NMR ($CDCl_3$, δ): 4.36 (dd, J = 5.2 Hz, J = 1.5 Hz, 2H, CH_2), 5.15-5.33 (m, 2H, CH_2=), 5.79-5.98 (m, 1H, CH=), 6.68 (m, 2H, Ar-H), 6.81 (d, J = 1.8 Hz, 1H, Ar-H).

2-Allyl-3,5-dichloro-phenol (4).



4

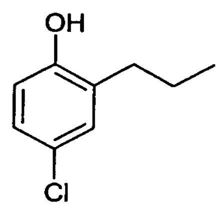
MW: 203.07; Yield: 66 %.

^{1}H-NMR ($CDCl_3$, δ): 3.49 (dm, J = 6.9 Hz, 2H, CH_2), 4.96-5.10 (m, 2H, CH_2=), 5.32 (s, 1H, OH), 5.74-5.94 (m, 1H, CH=), 6.65 (d, J = 2.0 Hz, 1H, Ar-H), 6.90 (d, J = 2.0 Hz, 1H, Ar-H).

General procedure for hydrogenation:

A solution of 10 mmol of the corresponding 2-allylphenols **3**, **4** in 80 mL of toluene and 30 mL of ethanol was hydrogenated for 5 hours at 30 psi, using Raney Ni as catalyst. The solution was filtered, concentrated under vacuum and purified by column chromatography (hexane/ethyl acetate) to afford the desired 2-propylphenols **5** and **6**.

4-Chloro-2-propyl-phenol (5).

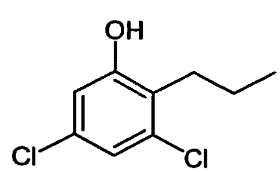


5

MW: 170.05; Yield: 70 %.

^{1}H-NMR ($CDCl_3$, δ): 0.90 (t, *J* = 7.3 Hz, 3H, CH_3), 1.56 (sext, *J* = 7.4 Hz, 2H, CH_2), 2.51 (t, *J* = 7.9 Hz, 2H, CH_2), 6.61 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.93 (m, 2H, Ar-H).

3,5-Dichloro-2-propyl-phenol (6).



6

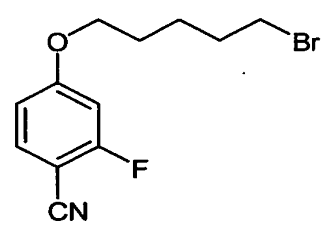
MW: 205.08; Yield: 90 %.

^{1}H-NMR ($CDCl_3$, δ): 0.89 (t, *J* = 7.3 Hz, 3H, CH_3), 1.49 (sext, *J* = 7.3 Hz, 2H, CH_2), 2.61 (t, *J* = 7.7 Hz, 2H, CH_2), 6.61 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.86 (d, *J* = 2.0 Hz, 1H, Ar-H).

General procedure for the synthesis of aryl 5-bromopentyl ethers 7-9.

A mixture of 10.22 mmol of the corresponding phenol, 20.45 mmol of 1,5-dibromopentane, 1.83 g (13.29 mmol) of anhydrous potassium carbonate and 138 mg (0.90 mmol) of sodium iodide in 19 mL of 2-butanone was refluxed for 48 hours. The resultant suspension was filtered, and the solution was evaporated to dryness and purified by column chromatography (hexane to hexane:ethyl acetate = 1:2, gradually), to afford a colorless oil.

4-(5-Bromo-pentyloxy)-2-fluoro-benzonitrile (7).

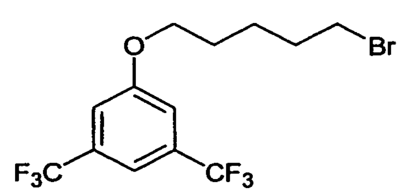


7

MW: 286.14; Yield: 56 %.

^{1}H-NMR ($CDCl_3$, δ): 1.41-1.65 (m, 2H, CH_2), 1.71-1.94 (m, 4H, $2CH_2$), 3.35 (t, J = 6.7 Hz, 2H, CH_2Br), 3.94 (t, J = 6.2 Hz, 2H, CH_2O), 6.59-6.71 (m, 2H, Ar-H), 7.44 (t, J = 8.1 Hz, 1H, Ar-H).

1-(5-Bromo-pentyloxy)-3,5-bis-trifluoromethyl-benzene (8).

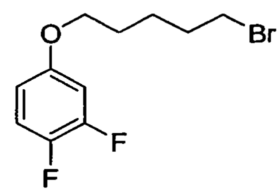


8

MW: 379.14; Yield: 12%.

^{1}H-NMR ($CDCl_3$, δ): 1.48-1.69 (m, 2H, CH_2), 1.70-1.95 (m, 4H, $2CH_2$), 3.37 (t, J = 6.6 Hz, 2H, CH_2Br), 3.97 (t, J = 6.2 Hz, 2H, CH_2O), 7.21 (s, 2H, Ar-H), 7.37 (s, 1H, Ar-H).

4-(5-Bromo-pentyloxy)-1,2-difluoro-benzene (9).



9

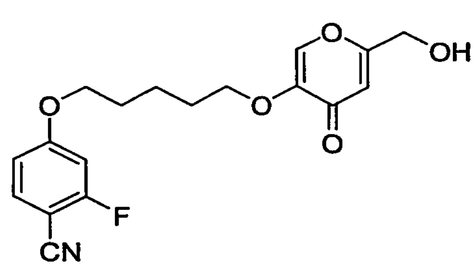
MW: 279.12; Yield: 23%.

^{1}H-NMR ($CDCl_3$, δ): 1.42-1.91 (m, 6H, $3CH_2$), 3.37 (t, J = 6.6 Hz, 2H, CH_2Br), 3.83 (t, J = 6.3 Hz, 2H, CH_2O), 6.41-6.65 (m, 2H, Ar-H), 6.98 (q, J = 9.2 Hz, 1H, Ar-H).

Synthesis of EHT 2904.

2-Fluoro-4-[5-(6-hydroxymethyl-4-oxo-4*H*-pyran-3-yloxy)-pentyloxy]-benzonitrile (EHT 2904).

A mixture of 0.88 mmol of **7**, 0.71 mmol of kojic acid and 0.22 g (1.6 mmol) of anhydrous potassium carbonate in 5 mL of anhydrous *N,N*-dimethylformamide was heated at 50 °C for 48 hours. The crude mixture was filtered and washed with ethyl acetate and the solvent was evaporated to dryness. The solid residue was then redissolved in ethyl acetate and filtered again. The solvent was concentrated and the product was purified by column chromatography (ethyl acetate) to raise 55.7 mg (95 %) of a white solid.



MW: 347.34; Yield: 95 %; Solid; Mp: 126-128 °C (Et_2O).

R$_f$: 0.1 (Hexane:EtOAc = 1:1).

IR (KBr, cm^{-1}): 3371, 3090, 2949, 2226, 1639, 1620, 1607, 1508, 1445, 1302, 1232, 1121, 1009, 920, 885, 849.

^{1}H-NMR ($CDCl_3$, δ): 1.51-1.68 (m, 2H, CH_2), 1.70-1.91 (m, 4H, 2xCH_2), 2.30 (br s, 1H, OH), 3.82 (t, J = 6.2 Hz, 2H, CH_2O), 3.95 (t, J = 6.1 Hz, 2H, CH_2O), 4.42 (s, 2H, C*H*$_2$OH), 6,47 (s, 1H, H_3), 6.59-6.70 (m, 2H, ArH), 7.39-7.51 (m, 2H, ArH, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.6, 28.7, 28.8, 61.1, 68.9, 69.7, 92.9 (d, J = 10.1 Hz, Ar<u>C</u>-CN), 102.9 (d, J = 22.9 Hz, ArCH), 111.8, 112.2, 114.6 (CN), 134.3, 139.6, 147.9, 164.2, (d, J = 11.0 Hz, ArC-O), 164.5 (d, J = 250.1 Hz, ArC-F), 174.8 (C=O).

Mass Spectrometry: 348 (M+1), 316, 211, 198, 179, 167, 155, 142, 126, 113, 95, 85, 69, 55, 41 (100).

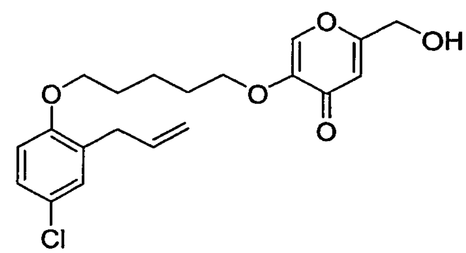
Elemental analysis for $C_{18}H_{18}FNO_5$

Calculated:	C, 62.24 %; H, 5.22 %; N, 4.03 %
Found:	C, 61.98 %; H, 5.37 %; N, 4.00 %

<u>Synthesis of Derivatives EHT 5431, EHT 6152, EHT 6978, EHT 2991.</u>

A suspension containing 10 mmol of the corresponding phenols **3-6**, 11 mmol of **1**, 13 mmol of potassium carbonate and 1 mmol of sodium iodide in 2-butanone was refluxed for 24 hours. After cooling the reaction mixture was filtrated and dried under reduce pressure. The reaction products were purified by column chromatography (hexane:ethyl acetate = 1:1).

<u>5-[5-(2-Allyl-4-chloro-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 5431).</u>



MW: 378.85; Yield: 90 %; Solid; Mp: 98-100 °C (Et_2O).

***R*f:** 0.2 (Hexane:EtOAc = 1:1).

[1]H-NMR ($CDCl_3$, δ): 1.49-1.62 (m, 2H, CH_2), 1.70-1.90 (m, 4H, $2xCH_2$), 3.06 (br s, 1H, OH), 3.26 (br d, *J* = 6.6 Hz, 2H, CH_2Ar), 3.79-3.90 (m, 4H, $2xCH_2O$), 4.43 (s, 2H, C<u>H2</u>OH), 4.99 (m, 2H, CH_2=), 5.76-5.96 (m, 1H, CH=), 6,53 (s, 1H, H_3), 6.64-6.76 (m, 1H, Ar-H), 7.02-7.16 (m, 2H, Ar-H), 7.54 (s, 1H, H_6).

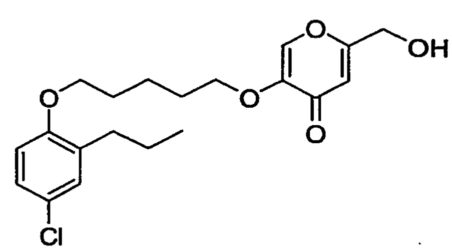
[13]C-NMR ($CDCl_3$, δ): 22.6, 28.8, 29.0, 34.1, 60.9, 68.0, 69.7, 111.8, 112.3, 115.9, 116.1, 125.0, 126.9, 129.3, 133.0, 136.1, 139.8, 147.7, 155.0, 167.7, 174.8.

Mass Spectrometry: 378 (M), 211, 169, 143, 127, 113, 95, 77, 69 (100), 55, 41.

Elemental analysis for $C_{20}H_{23}ClO_5$

Calculated:	C, 63.41 %; H, 6.12 %
Found:	C, 63.25 %; H, 6.50 %

<u>5-[5-(4-Chloro-2-propyl-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 6152).</u>



MW: 380.86; Yield: 91 %; Solid; Mp: 92-94 °C (Et_2O).

***R*f:** 0.1 (Hexane:EtOAc = 1:1).

IR (KBr, cm^{-1}): 3327, 2926, 1647, 1616, 1265, 1248, 1219.

^{1}H-NMR ($CDCl_3$, δ): 0.85 (t, J = 7.3 Hz, 3H, CH_3), 1.45-1.63 (m, 4H, 2xCH_2), 1.71-1.81 (m, 4H, 2CH_2), 2.47 (t, J = 7.2 Hz, 2H, CH_2Ar), 2.60 (br s, 1H, OH), 3.79-3.89 (m, 4H, 2xCH_2O), 4.42 (s, 2H, C*H*$_2$OH), 6,47 (s, 1H, H_3), 6.62-6.67 (m, 1H, Ar-H), 6.98-7.04 (m, 2H, Ar-H), 7.50 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 14.0, 22.6, 22.7, 28.8, 29.0, 32.1, 61.0, 67.9, 69.8, 112.1, 112.2, 125.0, 126.3, 129.6, 133.1, 139.7, 147.8, 155.5, 167.1, 174.8.

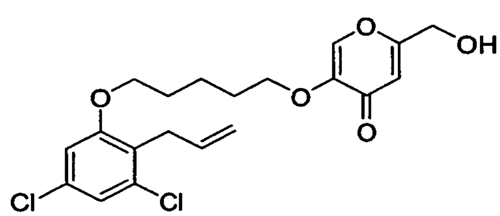
Mass Spectrometry: 380 (M), 378, 357, 346, 211, 195, 170, 155, 143 (100), 125, 113, 95, 77, 69, 41, 39.

Elemental analysis for $C_{20}H_{25}ClO_5$

Calculated: C, 63.07 %; H, 6.62%

Found: C, 62.67%; H, 6.92 %

5-[5-(2-Allyl-3,5-dichloro-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 6978).



MW: 413.29; Yield: 80 %; Solid; Mp: 59-61 °C (Et_2O).

***R$_f$*:** 0.13 (Hexane:EtOAc = 1:1).

^{1}H-NMR ($CDCl_3$, δ): 1.52-1.63 (m, 2H, CH_2), 1.72-1.90 (m, 4H, 2xCH_2), 3.00 (br s, 1H, OH), 3.41 (br s, 2H, CH_2Ar), 3.81 (t, J = 6.1 Hz, 2H, CH_2O), 3.83 (t, J = 6.3 Hz, 2H, CH_2O), 4.42 (s, 2H, C*H*$_2$OH), 4.86-4.96 (m, 2H, CH_2=), 5.68-5.88 (m, 1H, CH=), 6,46 (s, 1H, H_3), 6.66 (d, J = 1.9 Hz, 1H, Ar-H), 6.92 (d, J = 1.9 Hz, 1H, Ar-H), 7.51 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 22.7, 28.8, 28.9, 31.1, 61.1, 68.6, 69.8, 110.7, 112.2, 115.6, 121.4, 125.6, 132.7, 134.7, 135.5, 139.8, 148.0, 158.1, 167.4, 175.0.

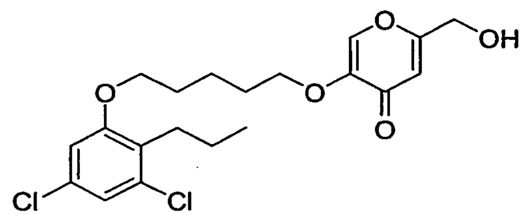
Mass Spectrometry: 412 (M-1), 241, 229, 211, 169, 155, 143, 127, 113, 95, 69 (100), 55, 41.

Elemental analysis for $C_{20}H_{22}Cl_2O_5$

Calculated: C, 58.12 %; H, 5.37 %

Found: C, 57.90 %; H, 5.56 %

5-[5-(3,5-Dichloro-2-propyl-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 2991).



MW: 415.31; Yield: 90 %; Solid; Mp: 77-79 °C (Et_2O).

***R_f*:** 0.2 (Hexane:EtOAc = 1:1).

IR (KBr, cm^{-1}): 3367, 2958, 2930, 2870, 1635, 1602, 1558, 1458, 1394, 1236, 1211, 1051.

^{1}H-NMR ($CDCl_3$, δ): 0.86 (t, J = 7.3 Hz, 3H, CH_3), 1.35-1.63 (m, 2H, CH_2), 1.72-1.86 (m, 4H, $2CH_2$), 2.62 (t, J = 7.3 Hz, 2H, CH_2Ar), 3.24 (br s, 1H, OH), 3.82 (t, J = 6.4 Hz, 2H, CH_2O), 3.87 (t, J = 6.1 Hz, 2H, CH_2O), 4.42 (s, 2H, CH_2OH), 6.48 (s, 1H, H_3), 6.63 (d, J = 1.9 Hz, 1H, Ar-H), 6.89 (d, J = 1.9 Hz, 1H, Ar-H), 7.52 (s, 1H, H_6).

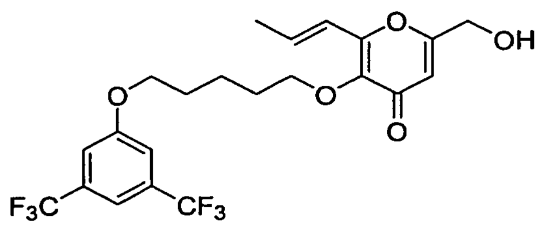
^{13}C-NMR ($CDCl_3$, δ): 14.1, 21.9, 22.5, 28.7, 28.8, 60.9, 68.3, 69.7, 110.4, 112.0, 121.2, 128.3, 131.9, 135.2, 139.8, 147.8, 158.1, 167.5, 174.9.

Mass Spectrometry: 414 (M-1), 399, 385, 365, 273, 245, 211, 193, 175, 155, 143 (100), 95, 85, 67, 53.

Synthesis of Derivatives EHT 5403, EHT 8307 and EHT 4112.

A mixture of 10 mmol of **7**, **8** or **9**, 11 mmol of (*E*)-3-hydroxy-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one and 13 mmol of potassium carbonate in 10 mL of anhydrous *N,N'*-dimethyformamide, was heated at 50° C for 48 hours. The crude mixture was filtered and washed with ethyl acetate and the solvent was evaporated to dryness. The product was purified by column chromatography (ethyl acetate) to raise the desired products.

<u>(*E*)- 3-[5-(3,5-Bis-trifluoromethyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 5403).</u>



MW: 480.40; Yield: 46 %; Solid; Mp: 90-92 °C (Et_2O).

R

IR (KBr, cm^{-1}): 3443, 3277, 2951, 2879, 1664, 1635, 1610, 1591, 1397, 1369, 1284, 1169, 1122.

^{1}H-NMR ($CDCl_3$, δ): 1.59-2.01 (m, 9H, CH_3, 3xCH_2), 2.58 (br s, 1H, OH), 4.10 (ap q, 4H, 2CH_2O), 4.54 (s, 2H, CH_2OH), 6.54-6.65 (m, 3H, H_5, 2xCH=), 7.29 (s, 2H, Ar-H), 7.45 (s, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 18.9, 22.5, 28.8, 29.7, 61.0, 68.8, 72.6, 112.3, 114.2, 114.7, 120.5, 124.0 (q, J = 272.5 Hz, 2xCF_3), 125.9, 132.9 (d, J = 33.4 Hz, CCF_3), 155.0, 157.0, 159.6, 166.1, 172.0, 176.7.

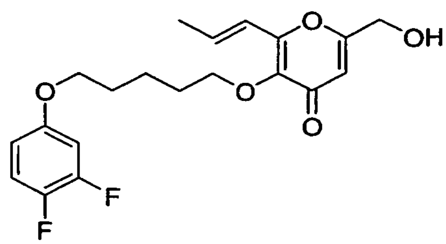
Mass Spectrometry: 480 (M), 465, 451, 425, 251, 237, 209, 195, 181, 167 (100), 135, 121, 95, 69, 55, 41.

Elemental analysis for $C_{22}H_{22}F_6O_5$

Calculated: C, 55.00 %; H, 4.62 %

Found: C, 54.62 %; H, 4.87 %

(*E*)- 3-[5-(3,4-Difluoro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 8307).



MW: 380.38; Yield: 69 %; Solid; Mp: 86-87 °C (Et_2O).

***R_f*:** 0.1 (Hexane:EtOAc = 1:1).

IR (KBr, cm^{-1}): 3265, 2992, 2852, 1662, 1635, 1601, 1581, 1213, 1161, 1091, 988.

^{1}H-NMR ($CDCl_3$, δ): 1.49-1.51 (m, 2H, CH_2), 1.52-1.80 (m, 4H, 2xCH_2), 1.86 (d, J = 4.8 Hz, 3H, CH_3), 3.61 (br s, 1H, OH), 3.84 (t, J = 6.2 Hz, 2H, CH_2O), 3.98 (t, J = 6.3 Hz, 2H, CH_2O), 4.40 (s, 2H, CH_2OH), 6.30-6.41 (m, 1H, H_5), 6.42-6.47 (m, 4H, 2CH=, 2xAr-H), 7.03 (q, J = 9.3 Hz, 1H, Ar-H).

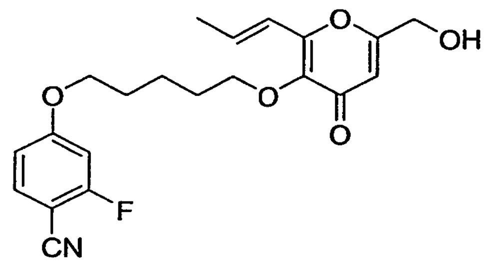
^{13}C-NMR ($CDCl_3$, δ): 18.9, 22.5, 28.9, 29.7, 61.9, 68.7, 72.6, 104.1 (d, J = 20.2 Hz, $C_{o,m}F$), 109.7 (dd, J = 6.0, 3.5 Hz, $C_{m,p}F$), 112.2, 117.1 (dd, J = 18.5, 2.6 Hz, $C_{o,m}F$), 118.8, 134.7, 141.5, 144.8 (dd, J = 239.5, 13.1 Hz, CF), 150.4 (dd, J = 248.0; 14.9 Hz, CF), 155.0, 155.4 (dd, J = 10.6, 4.7 Hz, $CO_{m,p}F$), 166.3, 176.8 (C=O).

Mass Spectrometry: 380 (M), 365, 351, 325, 285, 251, 237, 209, 195, 181, 165 (100), 143, 135, 113, 101, 83, 69, 55, 41.

Elemental analysis for $C_{20}H_{22}F_2O_5$

Calculated:	C, 63.15 %; H, 5.83 %
Found:	C, 63.61 %; H, 5.95 %

(*E*)-2-Fluoro-4-[5-(6-hydroxymethyl-4-oxo-2-propenyl-4*H*-pyran-3-yloxy)-pentyloxy]-benzonitrile (EHT 4112).



MW: 387.40; Yield: 60 %; Solid; Mp = 123-125 °C (Et_2O).

***Rf*:** 0.1 (Hexane:EtOAc = 1:1).

IR (KBr, cm^{-1}): 3430, 3240, 2870, 2230, 1662, 1622, 1603, 1506, 1439, 1300, 1234, 1205, 1178, 1121, 962.

^{1}H-NMR ($CDCl_3$, δ): 1.56-1.63 (m, 2H, CH_2), 1.71-1.88 (m, 7H, CH_3 and 2xCH_2), 2.73 (br s, 1H, OH), 3.93-4.03 (m, 4H, 2CH_2O), 4.42 (s, 2H, C*H*$_2$OH), 6.36-6.71 (m, 5H, H_5, 2xArH and 2xCH=), 7.39-7.47 (m, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 18.9, 22.3, 28.6, 29.6, 61.0, 68.9, 72.4, 92.8 (d, *J* = 10.1 Hz, Ar*C*-CN), 102.7 (d, *J* = 22.1 Hz), 111.7, 112.3, 114.4 (CN), 118.7, 126.5, 134.3 (d, *J* = 17.4 Hz, ArCH), 141.5, 154.8, 162.5, 164.0 (d, *J* = 250.0 Hz, ArC-F), 164.5 (d, J = 20 Hz), 165.6, 176.4 (C=O).

Mass Spectrometry: 387 (M), 372, 358, 326, 251, 237, 209, 195, 181, 167 (100), 150, 135, 120, 95, 83, 69, 55, 41.

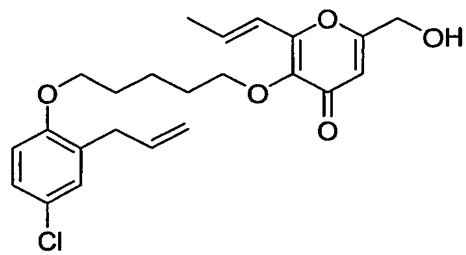
Elemental analysis for $C_{21}H_{22}FNO_5$

Calculated:	C, 65.11 %; H, 5.72 %; N, 3.62 %
Found:	C, 64.92 %; H, 5.64 %; N, 3.57 %

<u>Synthesis of Derivatives EHT 9226, EHT 1405, EHT 6506 and EHT 9916.</u>

A suspension containing 10 mmol of the corresponding phenols **3-6**, 11 mmol of **2**, 13 mmol of potassium carbonate and 1 mmol of sodium iodide in 2-butanone was refluxed for 24 hours. After cooling the reaction mixture was filtrated and dried under reduce pressure. The reaction products were purified by column chromatography (hexane / ethyl acetate 1:1).

(*E*)-3-[5-(2-Allyl-4-chloro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 9226).



MW: 418.91; Yield: 64 %; Yellowish oil.

***R_f*:** 0.2 (Hexane:EtOAc = 1:1)

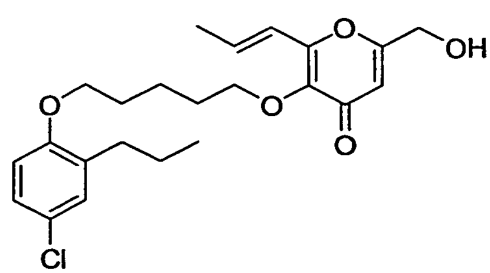
IR ($CHCl_3$, cm^{-1}): 3385, 2928, 2856, 1645, 1599, 1491, 1435, 1244.

^{1}H-NMR ($CDCl_3$, δ): 1.52-1.63 (m, 2H, CH_2), 1.72-1.86 (m, 4H, 2xCH_2), 1.91 (d, *J* = 4.0 Hz, 3H, CH_3), 2.21 (br s, 1H, OH), 3.31 (br d, *J* = 7.5 Hz, 2H, CH_2Ar), 3.39 (t, *J* = 6.1 Hz, 2H, CH_2O), 4.06 (t, *J* = 6.3 Hz, 2H, CH_2O), 4.47 (s, 2H, CH_2OH), 4.98-5.10 (m, 2H, CH_2=), 5.85-5.97 (m, 1H, CH=), 6.42 (s, 1H, H_5), 6.48-6.85 (m, 3H, 1Ar-H, 2xCH=), 7.07 (m, 2H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 19.0, 22.6, 29.1, 29.7, 34.2, 60.9, 68.2, 72.7, 112.1, 112.4, 116.2, 118.7, 125.2, 126.9, 129.6, 130.7, 134.9, 136.2, 141.4, 155.2, 155.3, 166.4, 176.8.

Mass Spectrometry: 418 (M), 403, 363, 251, 237, 209, 195, 167, 156, 135, 115, 103, 95, 69 (100), 55, 41.

(*E*)- 3-[5-(4-Chloro-2-propyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 1405).



MW: 420.93; Yield: 35 %, Yellowish oil.

R$_f$: 0.2 (Hexane:EtOAc = 1:1)

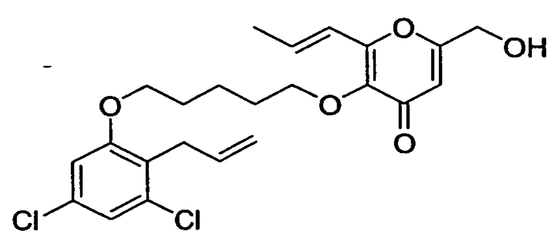
IR ($CHCl_3$, cm^{-1}): 3350, 2923, 2852, 1647, 1599, 1551, 1437, 1242.

^{1}H-NMR ($CDCl_3$, δ): 0.85 (t, J = 7.4 Hz, 3H, CH_3), 1.36-1.82 (m, 8H, 4xCH_2), 1.86 (d, J = 4.9 Hz, 3H, CH_3), 2.47 (t, J = 7.2 Hz, 2H, CH_2Ar), 3.51 (br s, 1H, OH), 3.87 (t, J = 6.1 Hz, 2H, CH_2O), 4.00 (t, J = 6.4 Hz, 2H, CH_2O), 4.42 (s, 2H, CH_2OH), 6.41 (s, 1H, H_5), 6.46-6.68 (m, 3H, 1Ar-H, 2xCH=), 6.80-7.04 (m, 2H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 14.0, 18.9, 22.6, 22.9, 29.1, 29.8, 32.2, 61.0, 68.1, 72.7, 112.1, 112.3, 118.8, 125.0, 126.4, 129.7, 133.2, 134.9, 141.5, 155.2, 155.6, 166.3, 176.6.

Mass Spectrometry: 420 (M), 405, 389, 251, 239, 209, 195, 183, 167, 141, 125, 107, 95, 69 (100), 55, 41.

(*E*)-3-[5-(2-Allyl-3,5-dichloro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 6506).



MW: 453.36; Yield: 88 %; Solid.

R$_f$: 0.1 (Hexane:EtOAc = 1:1).

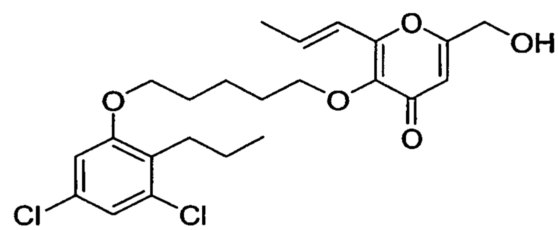
IR (KBr, cm^{-1}): 3414, 3221, 2930, 2852, 1643, 1599, 1560, 1439, 1232.

^{1}H-NMR ($CDCl_3$, δ): 1.78-2.21 (m, 9H, CH_3 and 3xCH_2), 2.92 (br s, 1H, OH), 3.86 (br d, J = 6.2 Hz, 2H, CH_2Ar), 4.16 (t, J = 6.1 Hz, 2H, CH_2O), 4.29 (t, J = 6.4 Hz, 2H, CH_2O), 4.74 (s, 2H, CH_2OH), 5.14-5.22 (m, 2H, CH_2=), 5.98-6.12 (m, 1H, CH=), 6.80-6.90 (m, 3H, H_5, 2xCH=), 6.93 (d, J = 1.8 Hz, 1H, Ar-H), 7.18 (d, J = 1.9 Hz, 1H, Ar-H).

^{13}**C-NMR (CDCl$_3$, δ)**: 18.8, 22.3, 28.7, 29.5, 30.8, 60.7, 68.5, 72.4, 110.5, 112.0, 115.3, 118.6, 121.1, 126.0, 132.4, 134.4 (3C), 134.6, 134.7, 154.9, 166.0, 176.5.

Mass Spectrometry: 452 (M-1), 437, 423, 363, 251, 235, 209, 183, 167 (100), 156, 135, 121, 95, 69, 55, 39.

(*E*)-3-[5-(3,5-Dichloro-2-propyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 9916).



MW: 455.37; Yield: 25 %; Solid; Mp: 91-93 °C (Hex / EtOAc).

***R$_f$*:** 0.1 (Hexane:EtOAc = 1:1).

IR (KBr, cm^{-1}): 3414, 3221, 2930, 2852, 1643, 1599, 1560, 1439, 1232.

^{1}**H-NMR (CDCl$_3$, δ):** 0.86 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.35-1.84 (m, 8H, 4xCH$_2$), 1.89 (d, *J* = 5.4 Hz, 3H, CH$_3$), 2.62 (t, *J* = 7.5 Hz, 2H, CH$_2$Ar), 3.42 (br s, 1H, OH), 3.87 (t, *J* = 6.1 Hz, 2H, CH$_2$O), 4.02 (t, *J* = 6.4 Hz, 2H, CH$_2$O), 4.46 (s, 2H, C*H$_2$*OH), 6.46-6.62 (m, 3H, 2xCH= and H$_5$), 6.64 (d, *J* = 2.0 Hz, 1H, ArH), 6.89 (d, *J* = 1.9 Hz, 1H, Ar-H).

^{13}**C-NMR (CDCl$_3$, δ)**: 14.2, 19.0, 22.1, 22.6, 28.9, 29.0, 29.8, 61.0, 68.6, 72.7, 110.5, 112.2, 118.8, 121.3, 128.4, 132.0, 134.9, 135.3, 141.5, 155.2, 158.2, 166.4, 176.8.

Mass Spectrometry: 455 (M), 454 (M-1), 439, 425, 413, 273, 251, 237, 209, 183, 167, 156, 135, 111, 95, 69, 53, 41 (100).

Elemental analysis for $C_{23}H_{28}Cl_2O_5$

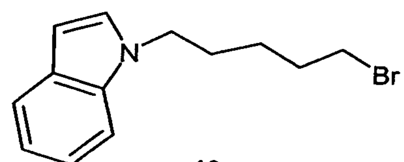
Calculated: C, 60.66 %; H, 6.20 %

Found: C, 60.49 %; H, 6.39 %

Synthesis of intermediate 10:

1-(5-bromopentyl)-1*H*-indole (10):

To a solution of dibromopentane (150 mmol) in 250 mL of DMF, 50 mmol of indole and 50 mmol of KOH were added. The reaction mixture was stirred at 30-40 °C overnight and then evaporated to dryness. The crude was purified by column chromatography in petroleum ether/diethyl ether to reach around 5 g (40 %) of a greenish oil (Dehaen, W. and Hassner, A. *J. Org. Chem. 56*, **1991**, 896).



10

MW: 266.18; Yield: 40%; Greenish oil.

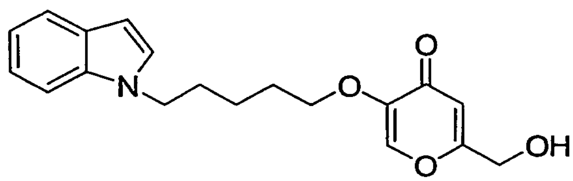
***R*f**: 0.2 (Hexane:Et_2O = 10:1).

^{1}H-NMR ($CDCl_3$, δ): 1.36-1.63 (m, 2H, CH_2), 1.88-2.03 (m, 4H, $2CH_2$), 3.45 (t, *J* = 6.7 Hz, 2H, CH_2Br), 4.23 (t, *J* = 7.0 Hz, 2H, CH_2N), 6.59 (d, *J* = 3.0 Hz, 1H, Ar-H), 7.16-7.45 (m, 4H, Ar-H), 7.73 (d, *J* = 7.7 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 25.7, 29.5, 32.4, 33.4, 46.2, 101.2, 109.3, 119.3, 121.1, 121.5, 127.8, 128.7, 136.0.

2-Hydroxymethyl-5-(5-indol-1-yl-pentyloxy)-4*H*-pyran-4-one (EHT 6353).

To a solution of 1-(5-bromopentyl)-1*H*-indole **10** (0.84 mmol) in 4 mL of DMF, 0.84 mmol of kojic acid, 1.69 mmol of Cs_2CO_3 and 0.07 mmol of NaI were added. The reaction mixture was stirred for 3 hours at room temperature, under Ar atmosphere. The crude was filtered and evaporated to dryness. The reaction product was purified by column chromatography (ethyl acetate/hexane) and crystallized in ethyl acetate to reach an 85 % of the desired pyranone.



MW: 327.37; Yield: 85 %.

R_f: 0.2 (Et_2O / MeOH, 8:2).

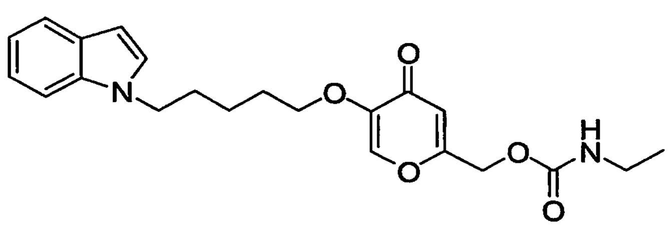
^{1}H-NMR ($CDCl_3$, δ): 1.20-1. 36 (m, 2H, CH_2), 1.56-1.79 (m, 4H, 2xCH_2), 2.39 (br s, 1H, OH), 3.60 (t, J = 6.4 Hz, 2H, CH_2N), 3.97 (t, J = 6.9 Hz, 2H, CH_2O), 4.29 (s, 2H, CH_2OH), 6.30 (d, J = 3.1 Hz, 1H, Ar-H), 6.35 (s, 1H, H_3), 6.87-7.18 (m, 5H, 4 Ar-H and H_6), 7.45 (d, J = 7.6 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.5, 28.8, 30.1, 46.4, 61.0, 69.6, 101.2, 109.5, 112.1, 119.4, 121.1, 121.5, 128.0, 128.8, 139.6, 147.9, 167.4, 174.9.

<u>General procedure for the synthesis of the aryl carbamates EHT 1120 and EHT 6231.</u>

The corresponding alkyl isocyanate (1.0 mmol) is added to a green heterogeneous mixture of the alcohol **EHT 6353** (1.0 mmol), reagent grade CuCl (1.0 mmol), and dry DMF (5 mL) at room temperature. Disappearance of the starting material is followed by TLC (4 -16 hours). The reaction crude is diluted with Et_2O (20 mL), washed with H_2O (10 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated. The final products were purified by column chromatography (EtOAc/Hexane) and crystallized in EtOAc/petroleum ether.

<u>Ethyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 1120).</u>



MW: 398.45; Yield: 25 %; Solid; Mp: 81-83 °C.

R$_f$: 0.4 (EtOAc).

IR (KBr, cm^{-1}): 3319, 3070, 2932, 2872, 1732, 1647, 1624, 1541, 1252, 1213, 741.

^{1}H-NMR ($CDCl_3$, δ): 1.09 (t, J = 7.2 Hz, 3H, CH_3), 1.32-1.47 (m, 2H, CH_2), 1.67-1.90 (m, 4H, 2xCH_2), 3.11-3.25 (m, 2H, CH_2NH), 3.72 (t, J = 6.4 Hz, 2H, CH_2N), 4.07 (t, J = 6.9 Hz, 2H, CH_2O), 4.81 (s, 3H, CH_2OCO, NH), 6.33 (s, 1H, H_3), 6.41 (d, J = 3.1 Hz, 1H, Ar-H), 6.98-7.29 (m, 4H, Ar-H), 7.40 (s, 1H, H_6), 7.55 (d, J = 7.6 Hz, 1H, Ar-H).

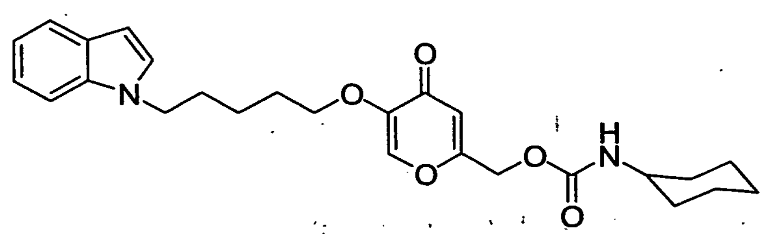
^{13}C-NMR ($CDCl_3$, δ): 15.3, 23.5, 28.8, 30.1, 36.3, 46.3, 61.5, 69.5, 101.1, 109.5, 113.4, 119.3, 121.1, 121.5, 127.9, 128.7, 136.0, 139.5, 148.1, 155.0, 161.2, 174.3.

Mass Spectrometry: 399.4 (M+1), 421.4 (M+ Na).

Elemental analysis for $C_{22}H_{26}N_2O_5$

Calculated:	C, 66.32 %; H, 6.58 %; N, 7.03 %
Found:	C, 66.23 %; H, 6.43 %; N, 7.06 %

<u>Cyclohexyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 6231).</u>



MW: 452.54; Yield: 77 %; Solid; Mp: 78-80 °C.

***R$_f$*:** 0.7 (EtOAc).

IR (KBr, cm^{-1}): 3325, 2933, 1734, 1684, 1570, 1234, 1215, 742.

^{1}H-NMR ($CDCl_3$, δ): 0.89-1.79 (m, 16H, 8xCH_2), 3.20-3.45 (m, 1H, CHNH), 3.62 (t, *J* = 6.4 Hz, 2H, CH_2N), 3.97 (t, *J* = 6.9 Hz, 2H, CH_2O), 4.62 (d, *J* = 9.9 Hz, 1H, NH), 4.69 (s, 2H, CH_2OCO), 6.23 (s, 1H, H_3), 6.30 (d, *J* = 2.8 Hz, 1H, Ar-H), 6.87-7.18 (m, 4H, Ar-H), 7.29 (s, 1H, H_6), 7.44 (d, *J* = 7.5 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.2, 24.5, 25.2, 28.5, 29.7, 33.1, 46.0, 50.1, 60.2, 69.2, 100.8, 109.1, 110.4, 119.0, 120.8, 121.2, 127.6, 127.8, 136.0, 139.5, 147.0, 163.5, 175.0.

Mass Spectrometry: 453.1 (M+1), 475.1 (M+ Na).

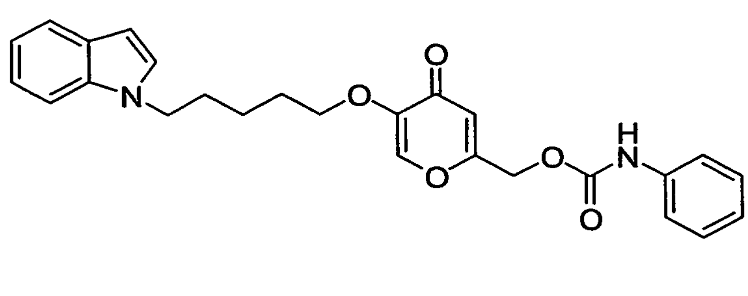
Elemental analysis for $C_{26}H_{32}N_2O_5$

Calculated:	C, 69.01 %; H, 7.13 %; N, 6.19 %
Found:	C, 68.69 %; H, 7.09 %; N, 6.16 %

General procedure for the synthesis of the aryl carbamates EHT 4902, EHT 2232 and EHT 5332.

To a solution of 0.74 mmol of the corresponding aryl isocyanate in 1.7 mL of THF, another solution of the alcohol **EHT 6353** in triethylamine is added dropwise. The reaction mixture is stirred at room temperature during 24 hours and then dried concentrated under reduced pressure. The final products were purified by column chromatography using hexane/ethyl acetate as eluent and crystallized in EtOAc/petroleum ether.

Phenyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 4902).



MW: 446.50; Yield: 77 %; Solid; Mp: 150 °C (dec.).

***R_f*:** 0.3 (EtOAc).

IR (KBr, cm^{-1}): 3448, 3259, 3084, 2949, 2930, 1730, 1647, 1616, 1553, 1448, 1238, 748.

^{1}H-NMR (DMSO-d_6, δ): 1.33-1.49 (m, 2H, CH_2), 1.70-1.91 (m, 4H, 2xCH_2), 3.84 (t, J = 6.4 Hz, 2H, CH_2N), 4.25 (t, J = 7.0 Hz, 2H, CH_2O), 5.08 (s, 2H, CH_2OCO), 6.47 (d, J = 3.1 Hz, 1H, Ar-H), 6.53 (s, 1H, H_3), 7.02-7.21 (m, 3H, Ar-H), 7.32-7.61 (m, 7H, Ar-H), 8.21 (s, 1H, H_6).

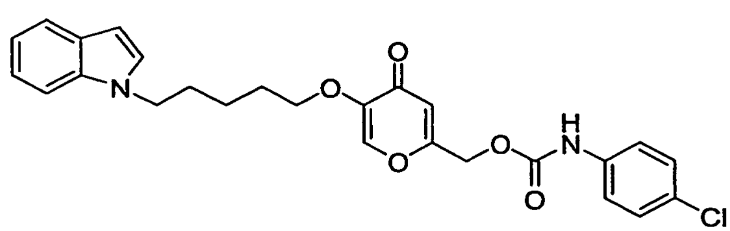
^{13}C-NMR ($CDCl_3$, δ): 23.9, 28.0, 29.8, 45.8, 61.0, 69.9, 100.5, 109.9, 112.7, 118.6, 121.3, 121.5, 124.2, 127.1, 128.8, 138.7, 141.1, 174.9.

Mass Spectrometry: 445.5 (M-1).

Elemental analysis for $C_{26}H_{26}N_2O_5$

Calculated:	C, 69.94 %; H, 5.87 %; N, 6.27 %
Found:	C, 69.76 %; H, 5.80 %; N, 6.07 %

(4-Chloro-phenyl)-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2232).



MW: 480.94; Yield: 30 %; Solid; Mp: 170-171 °C.

***R_f*:** 0.2 (EtOAc).

IR (KBr, cm^{-1}): 3448, 3286, 2932, 1734, 1701, 1655, 1549, 1271, 1243.

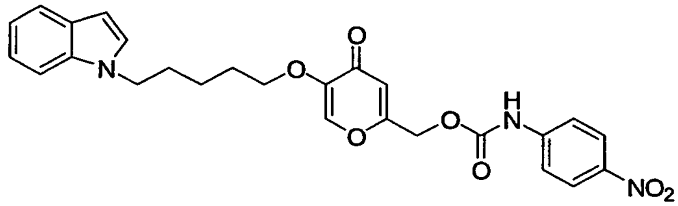
^{1}H-NMR ($CDCl_3$/DMSO-d_6, δ): 1.30-1.50 (m, 2H, CH_2), 1.68-1.96 (m, 4H, 2xCH_2), 3.74 (t, J = 6.4 Hz, 2H, CH_2N), 4.08 (t, J = 7.0 Hz, 2H, CH_2O), 4.92 (s,

2H, CH_2OCO), 6.38 (d, J = 3.0 Hz, 1H, Ar-H), 6.43 (s, 1H, H_3), 6.95-7.50 (m, 9H, Ar-H), 7.54 (s, 1H, H_6), 9.44 (br s, 1H, NH).

^{13}C-NMR ($CDCl_3$, δ): 23.4, 28.7, 29.7, 29.9, 46.2, 61.8, 69.4, 101.0, 109.5, 113.8, 119.2, 120.0, 120.9, 121.4, 127.8, 129.2, 139.4, 148.1, 174.0.

Mass Spectrometry: 481.0 (M+1), 503.0 (M+ Na).

(4-Nitro-phenyl)-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 5332).



MW: 491.49; Yield: 30 %; Solid; Mp: 135-137° C.

***R$_f$*:** 0.6 (EtOAc).

IR ($CHCl_3$, cm^{-1}): 3377, 1709, 1653, 1514, 1337.

^{1}H-NMR ($CDCl_3$, δ): 1.30-1.43 (m, 2H, CH_2), 1.72-1.82 (m, 4H, 2xCH_2), 3.75 (t, J = 6.3 Hz, 2H, CH_2N), 4.08 (t, J = 6.9 Hz, 2H, CH_2O), 5.34 (s, 2H, CH_2OCO), 6.40 (s, 1H, H_3), 6.49 (s, 1H, Ar-H), 7.01-7.12 (m, 3H, Ar-H), 7.25-7.27 (m, 2H, Ar-H), 7.45-7.60 (m, 3H, 2Ar-H, H_6), 7.80 (br s, 1H, NH), 8.10-8.15 (m, 2H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.4, 28.7, 30.0, 46.3, 69.4, 101.1, 109.1, 119.3, 121.0, 121.5, 124.7, 127.5, 135.0, 139.1, 144.6, 147.8, 173.6.

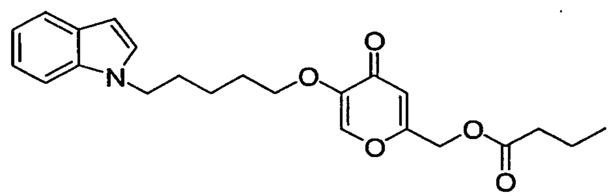
Elemental analysis for $C_{26}H_{25}N_3O_7$

Calculated:	C, 63.54 %; H, 5.13 %; N, 8.55 %
Found:	C, 63.45 %; H, 4.97 %; N, 8.25 %

Synthesis of the esters EHT 1393, EHT 2253, EHT 2665, EHT 6517, EHT 4167 and EHT 0078.

To a solution of the corresponding acid (0.62 mmol) in CH_2Cl_2 (0.62 mL) under an argon atmosphere, was added a solution of alcohol **EHT 6353** (0.92 mmol) in CH_2Cl_2 (0.92 mL). The reaction mixture was cooled at 0° C, while preparing a mixture of DCC (0.62 mmol) and DMAP (0.04 mmol) in CH_2Cl_2 (10 mL), which was then added with continuous stirring at 0° C during 5 minutes. The reaction was left to reach room temperature and stirred overnight. The mixture was evaporated and then diluted with AcOEt. The organic phase was washed with water, dried over $MgSO_4$ and evaporated to afford the esters, which were purified by column chromatography (hexane:AcOEt = 1:1).

Butanoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 1393).



MW: 397.46; Yield: 55 %; Oil.

***Rf*:** 0.1 (Hexane:EtOAc = 1:1).

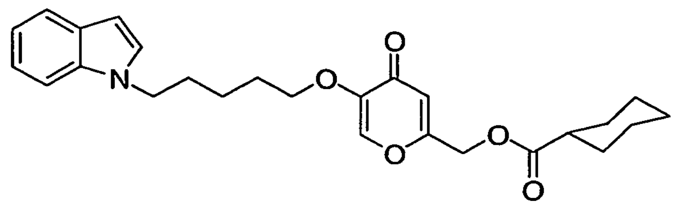
IR ($CHCl_3$, cm^{-1}): 2937, 1743, 1653, 1464, 1169.

^{1}H-NMR ($CDCl_3$, δ): 0.89 (t, J = 7.4 Hz, 3H, CH_3), 1.10-1.22 (m, 2H, CH_2), 1.31-1.46 (m, 2H, CH_2), 1.52-1.89 (m, 4H, 2CH_2), 2.30 (t, J = 7.4 Hz, 2H, CH_2COO), 3.68 (t, J = 6.4 Hz, 2H, CH_2N), 4.06 (t, J = 6.9 Hz, 2H, CH_2O), 4.81 (s, 2H, CH_2OCO), 6.34 (s, 1H, H_3), 6.40 (d, 1H, J = 3.0 Hz, 1H, Ar-H), 6.97-7.28 (m, 4H, Ar-H), 7.39 (s, 1H, H_6), 7.55 (d, J = 7.6 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 13.6, 18.3, 23.4, 28.7, 29.9, 35.7, 46.2, 60.9, 69.4, 101.0, 109.3, 113.7, 119.2, 121.0, 121.4, 127.8, 128.6, 135.9, 139.4, 148.0, 161.6, 172.5, 174.0.

Mass Spectrometry: 398.1 (M+1), 420.1 (M+Na).

Cyclohexanecarboxylic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2253).



MW: 437.53; Yield: 21 %; Solid; Mp: 62-66 °C.

R$_f$: 0.5 (EtOAc:hexane = 8:2).

IR (KBr, cm^{-1}): 3421, 2932, 2854, 1736, 1655, 1637, 1263, 1242, 1213, 748.

^{1}H-NMR ($CDCl_3$, δ): 1.20-1.47 (m, 8H, 4xCH_2), 1.48-1.95 (m, 8H, 4xCH_2), 2.25-2.38 (m, 1H, CHCO), 3.73 (t, *J* = 6.4 Hz, 2H, CH_2N), 4.08 (t, *J* = 6.9 Hz, 2H, CH_2O), 4.81 (s, 2H, CH_2OCO), 6.34 (s, 1H, H_3), 6.41 (d, *J* = 3.1 Hz, 1H, Ar-H), 6.99-7.29 (m, 4H, ArH), 7.40 (s, 1H, H_6), 7.56 (d, *J* = 7.7 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.3, 25.2, 25.5, 28.6, 28.8, 29.8, 42.8, 46.1, 60.7, 69.3, 100.9, 109.2, 113.4, 119.1, 120.9, 121.2, 127.7, 135.3, 139.3, 147.2, 161.8, 174.1, 180.0.

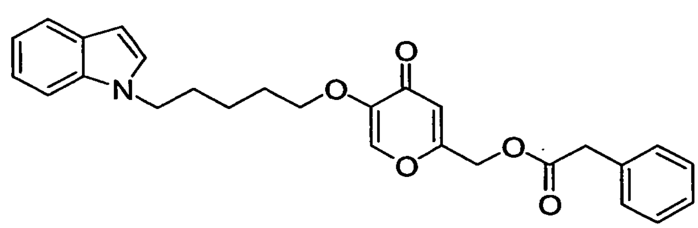
Mass Spectrometry: 438.1 (M+1), 460.1 (M+ Na).

Elemental analysis for $C_{26}H_{31}NO_5$

Calculated: C, 71.37 %; H, 7.14 %; N, 3.20 %

Found: C, 71.55 %; H, 6.77 %; N, 3.12 %

Phenyl-acetic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2665).



MW: 445.51; Yield: 62 %; Oil.

R$_f$: 0.3 (hexane:EtOAc = 1:1).

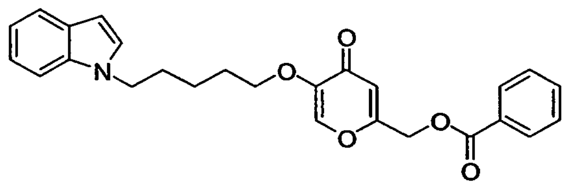
IR ($CHCl_3$ cm^{-1}): 3018, 2941, 1747, 1653, 1159.

^{1}H-NMR ($CDCl_3$, δ): 1.35-1.47 (m, 2H, CH_2), 1.68-1.90 (m, 4H, 2xCH_2), 3.64 (s, 2H, CH_2COO), 3.72 (t, J = 6.4 Hz, 2H, CH_2N), 4.08 (t, J = 6.9 Hz, 2H, CH_2O), 4.83 (s, 2H, CH_2OCO), 6.30 (s, 1H, H_3), 6.41 (d, J = 3.1 Hz, 1H, Ar-H), 6.97-7.31 (m, 9H, Ar-H), 7.37 (s, 1H, H_6), 7.56 (d, J = 7.7 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.4, 28.7, 29.9, 40.9, 46.2, 61.5, 69.5, 101.0, 109.3, 113.9, 119.2, 121.0, 121.4, 127.5, 127.8, 128.6, 128.8, 129.3, 132.0, 135.9, 139.4, 148.0, 161.2, 170.0, 174.0.

Mass Spectrometry: 446.0 (M+1), 468.0 (M+Na).

Benzoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 6517).



MW: 431.48; Yield: 62 %; Solid; Mp: 71-73 °C.

***R_f*:** 0.2 ($CHCl_3$).

IR (KBr, cm^{-1}): 2920, 1730, 1718, 1649, 1626, 1601, 1452, 1261, 1215, 735, 714.

^{1}H-NMR ($CDCl_3$, δ): 1.32-1.47 (m, 2H, CH_2), 1.68-1.90 (m, 4H, 2xCH_2), 3.73 (t, J = 6.4 Hz, 2H, CH_2N), 4.07 (t, J = 6.9 Hz, 2H, CH_2O), 5.07 (s, 2H, CH_2OCO), 6.40 (d, J = 2.5 Hz, 1H, Ar-H), 6.41 (s, 1H, H_3), 7.46-7.59 (m, 9H, Ar-H), 7.98 (d, J = 3.6 Hz, 1H, Ar-H), 8.03 (s, 1H, H_6).

^{13}C-NMR ($CDCl_3$, δ): 23.2, 28.5, 29.4, 37.4, 46.0, 61.3, 69.2, 100.8, 109.2, 113.5, 119.0, 120.7, 121.2, 127.6, 128.4, 129.7, 133.6, 139.1, 148.2, 161.6, 174.1.

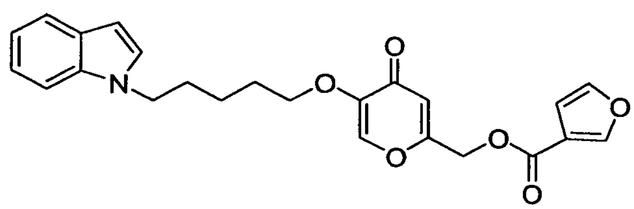
Mass Spectrometry: 432.8 (M+1), 454.5 (M+ Na).

Elemental analysis for $C_{26}H_{25}NO_5$

Calculated: C, 72.37 %; H, 5.84 %; N, 3.25 %

Found: C, 72.76 %; H, 5.80 %; N, 3.07 %

Furan-3-carboxylic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 4167).



MW: 421.44; Yield: 35 %; Solid; Mp: 103-105 ° C (dec.).

***R_f*:** 0.2 ($CHCl_3$).

IR (KBr, cm^{-1}): 3329, 3086, 3057, 2932, 1720, 1649, 1628, 1315, 1165, 968, 739.

^{1}H-NMR ($CDCl_3$, δ): 1.34-1.47 (m, 2H, CH_2), 1.68-1.90 (m, 4H, 2xCH_2), 3.73 (t, J = 6.4 Hz, 2H, CH_2N), 4.07 (t, J = 6.9 Hz, 2H, CH_2O), 4.99 (s, 2H, CH_2OCO), 6.40 (s, 2H, H_3, Ar-H), 6.70 (d, J = 1.3 Hz, 1H, Ar-H), 6.99-7.28 (m, 4H, Ar-H), 7.39-7.42 (m, 2H, Ar-H, H_6), 7.55 (d, J = 7.7 Hz, 1H, Ar-H), 8.01 (d, J = 0.7 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.2, 28.5, 29.7, 46.0, 60.7, 69.2, 100.8, 109.1, 109.5, 113.6, 117.2, 119.0, 120.8, 121.2, 127.6, 128.4, 135.1, 139.2, 144.0, 148.3, 161.2, 161.3, 173.8.

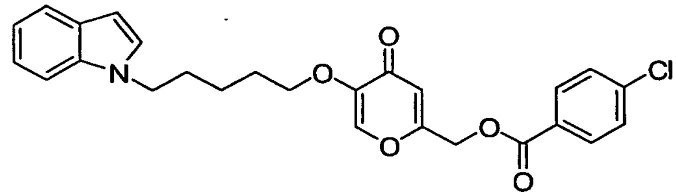
Mass Spectrometry: 444.1 (M+1).

Elemental analysis for $C_{24}H_{23}NO_6$

Calculated: C, 68.40 %; H, 5.53 %; N, 3.32 %

Found: C, 68.57 %; H, 5.73 %; N, 3.70 %

4-Chloro-benzoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 0078).



MW: 465.93; Yield: 55 %; Solid; Mp: 215-220 ° C.

R_f: 0.2 ($CHCl_3$:hexane = 8:2).

IR (KBr, cm^{-1}): 3113, 3092, 2951, 1718, 1645, 1626, 1283, 1261, 1217, 1109, 739.

^{1}H-NMR ($CDCl_3$, δ): 1.36-1.47 (m, 2H, CH_2), 1.69-1.87 (m, 4H, 2xCH_2), 3.74 (t, *J* = 6.4 Hz, 2H, CH_2N), 4.08 (t, *J* = 6.9 Hz, 2H, CH_2O), 5.06 (s, 2H, CH_2OCO), 6.41 (d, *J* = 3.1 Hz, 1H, Ar-H), 6.44 (s, 1H, H_3), 6.98-7.43 (m, 7H, 6Ar-H, H_6), 7.55 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.90-7.96 (m, 2H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 23.6, 28.3, 30.0, 45.2, 61.8, 64.9, 101.2, 109.5, 114.1, 119.3, 121.2, 121.6, 127.3, 129.2, 131.4, 136.1, 139.4, 147.9, 160.8.

Mass Spectrometry: 466.1 (M+1), 488.1 (M+Na).

Elemental analysis for $C_{26}H_{24}ClNO_5$

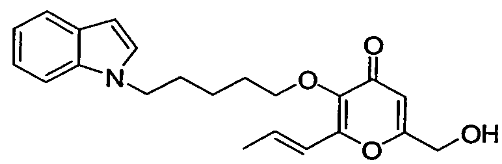
Calculated:	C, 67.02 %; H, 5.19 %; N, 3.01 %
Found:	C, 67.35 %; H, 5.36 %; N, 3.00 %

<u>Synthesis of EHT 7286.</u>

<u>(*E*)-6-Hydroxymethyl-3-(5-indol-1-yl-pentyloxy)-2-propenyl-4*H*-pyran-4-one (EHT 7286).</u>

To a solution of 1-(5-bromopentyl)-1*H*-indole **10** (0.84 mmol) in 4 mL of DMF, 0.84 mmol of 2-allyl-3-hydroxy-6-hydroxymethyl-4*H*-pyran-4-one, 1.69 mmol of Cs_2CO_3 and 0.07 mmol of NaI were added. The reaction mixture was stirred for 3 hours at room temperature, under an argon atmosphere. The crude was filtered and evaporated to dryness. The reaction product was purified by column

chromatography (ethyl acetate:hexane) and crystallized in ethyl acetate to reach an 80 % of the desired pyranone.



MW: 367.44; Yield: 80 %, solid; Mp = 62-64° C.

R_f: 0.4 (Et_2O:MeOH = 8:2).

IR (KBr, cm^{-1}): 3402, 3215, 3051, 2926, 2852, 1655, 1641, 1593, 1439, 1311, 1194, 737.

^{1}H-NMR ($CDCl_3$, δ): 1.48-1.60 (m, 2H, CH_2), 1.74-2.10 (m, 4H, 2xCH_2), 1.98 (d, *J* = 5.2 Hz, 3H, CH_3), 2.64 (br s, 1H, OH), 4.07 (t, *J* = 6.6 Hz, 2H, CH_2N), 4.21 (t, *J* = 7.0 Hz, 2H, CH_2O), 4.54 (s, 2H, CH_2OH), 6.47-6.61 (m, 3H, 2xCH=, H_5), 7.11-7.43 (m, 5H, Ar-H), 7.69 (d, *J* = 7.6 Hz, 1H, Ar-H).

^{13}C-NMR ($CDCl_3$, δ): 18.7, 23.2, 29.8, 46.1, 60.8, 72.2, 100.8, 109.1, 112.1, 118.5, 119.0, 120.8, 121.1, 127.6, 127.8, 134.3, 136.0, 141.7, 154.9, 165.0, 175.8.

Mass Spectrometry: 367 (M), 251, 237, 209, 185, 170, 156, 144, 130 (100), 117, 103, 77, 69, 53, 39.

Elemental analysis for $C_{22}H_{25}NO_4$

Calculated:	C, 71.91 %; H, 6.86 %; N, 3.81 %
Found:	C, 71.51 %; H, 6.92 %; N, 3.90 %

Synthesis of Derivatives EHT 7286, EHT 7395, EHT 1414, EHT 2939, EHT 6245, EHT 1329, EHT 0696, EHT 1593, EHT 1171, EHT 3663, EHT 1074, EHT 4408, EHT 5810, EHT 0470, EHT 7565, EHT 5230, EHT 9411, EHT 7151, EHT 7096, EHT 9013, EHT 6060, EHT 5769, EHT 7976, EHT 6448, EHT 2427, EHT 8309, EHT 5457, EHT 5235, EHT 8617, EHT 0091, EHT 8140, EHT 7337, EHT 9376, EHT 0407, EHT 0823, EHT 0533 and EHT 9387.

General procedures.

Method A (in THF):

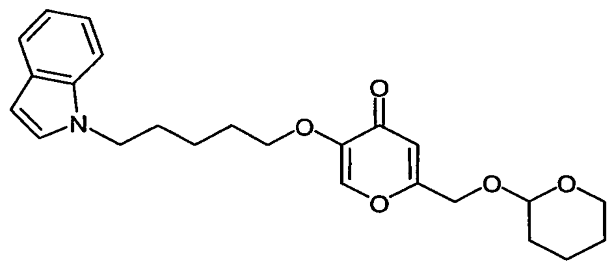
In a 25 mL round-bottom flask equipped with a magnetic stirrer and under an inert atmosphere were charged successively one equivalent of NaH (60 % in mineral oil), anhydrous THF (10 mL) and the monomer to be deprotonated (250 mg). The reaction mixture was abandoned until no evolution of gas was observed (between 3 and 5 hours). A solution 1 M of 5-(5-bromo-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **14** in THF (1 eq) was added and the reaction mixture was stirred 12 h at room temperature. The reaction mixture is evaporated *in vacuo*, the crude product is purified by a wash with a solution of aqueous NaOH 2N and/or by flaschromatography on silica.

Method B (in DMSO):

In a 50 mL round-bottom flask equipped with a magnetic stirrer and under an inert atmosphere were charged successively one equivalent of NaH (60 % in mineral oil), DMSO (5 mL) and the monomer to be deprotonated (250 mg). The reaction mixture was heated at 60 °C for 3 hours. After cooling to room temperature, the 5-(5-bromo-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **14** (1 eq) was added (in one time) and the reaction mixture was heated at 60 °C for 12 h. After cooling, 50 mL of dichloromethane was added, the organic layer is washed with H_2O (4 x 10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product is purified by a wash with a solution of aqueous NaOH 2N and/or by flaschromatography on silica.

5-(5-Indol-1-yl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7395).

The compound was prepared according to method A with indol (0.25 g, 2.13 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 99:1 an amber oil **EHT 7395** (0.46 g, 53 % yield) was obtained.

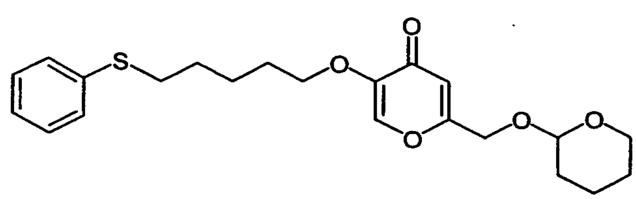


MW: 411.49; Yield: 53 %; Amber oil.

^{1}H-NMR ($CDCl_3$, δ): 1.63-1.98 (m, 12H, 6xCH_2), 3.45 (t, J = 5.4 Hz, 2H, -NCH_2), 3.52-3.60 (m, 1H, CH_2CH_2O), 3.81 (t, J = 6.6 Hz, 2H, OCH_2), 3.84-3.98 (m, 1H, CH_2CH_2O), 4.28 (d, J_{BA} = 14.4 Hz, 1H, CH_2O), 4.38 (d, J_{AB} = 14.4 Hz, 1H, CH_2O), 4.72-4.77 (m, 1H, OCHO), 6.32 (s, 1H, -C=CH-), 6.76 (d, J = 3.6 Hz, 1H, Ind-H), 7.24-7.36 (m, 2H, Ind-H), 7.57 (d, J = 7.8 Hz, 1H, Ind-H), 7.63 (d, J = 7.8 Hz, 1H, Ind-H), 7.87 (s, 1H, -C=CH-), 8.03 (d, J = 3.6 Hz, 1H, Ind-H).

5-(5-Phenylsulfanyl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 1414).

The compound was prepared according to method A with benzenethiol (0.25 g, 2.27 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 99:1 a yellow oil **EHT 1414** (0.55 g, 63 % yield) was obtained.



MW: 404.52; Yield 63 %; Yellow oil.

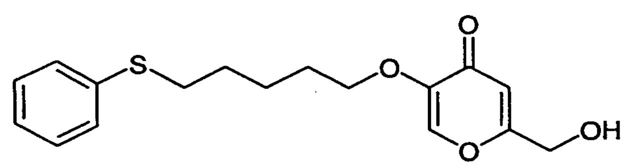
^{1}H-NMR ($CDCl_3$, δ): 1.50-1.95 (m, 12H, 6xCH_2), 2.95 (t, 2H, J = 4.8 Hz, SCH_2), 3.50-3.58 (m, 1H, CH_2CH_2O), 3.82-3.90 (m, 3H, CH_2CH_2O and OCH_2), 4.34 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.53 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.71-4.75 (m, 1H, OCHO), 6.52 (d, J = 0.6 Hz, 1H, -C=CH-), 7.14-7.36 (m, 5H, Ar-H), 7.56 (s, 1H, -C=CH-).

MS-ESI *m/z* (rel. int.): 405.0 ($[MH]^+$, 15), 179.0 (100).

HPLC: Method A, detection UV 254 nm, **EHT 1414** RT = 6.64 min, peak area 93.2 %.

2-Hydroxymethyl-5-(5-phenylsulfanyl-pentyloxy)-4*H*-pyran-4-one (EHT 2939).

EHT 1414 in MeOH and activated DOWEX (50WX8) were stirred 2 h at room temperature. The suspension was filtered and the precipitate was washed MeOH. After evaporation a brown solid **EHT 1329** (65 % yield) was obtained.



MW: 320.40; Yield: 65 %; Brown solid; Mp = 98.6 °C.

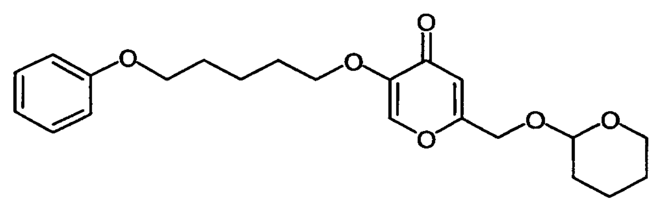
^{1}H-NMR ($CDCl_3$, δ): 1.45-1.90 (m, 4H, 2xCH_2), 2.93 (t, 2H, J = 7.0 Hz, 2H, -SCH_2), 3,15 (s broad, 1H, OH), 3.83 (t, 2H, J = 6.5 Hz, 2H, OCH_2), 4.47 (s, 1H, CH_2OH), 6.51 (s, 1H, -C=CH-), 7.12-7.21 (m, 1H, Ar-H), 7.22-7.26 (m, 4H, Ar-H), 7.54 (s, 1H, -C=CH-).

MS-ESI *m/z* (rel. int.): 321.0 ($[MH]^+$,), 179.0 (100).

HPLC: Method A, detection UV 254 nm, **EHT 2939** RT = 5.27 min, peak area 90.7 %.

5-(5-Phenoxy-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6245).

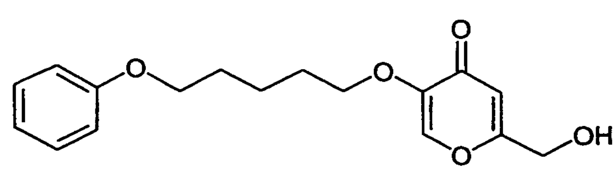
The compound was prepared according to method A with phenol (0.25 g, 2.65 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:1 a brown solid **EHT 6245** (0.78 g, 76 % yield) was obtained.



MW: 388.45; Yield 76 %; Brown solid; Mp = 54.4 °C.
^{1}H-NMR ($CDCl_3$, δ): 1.50-1.99 (m, 12H, 6xCH_2), 3.50-3.58 (m, 1H, CH_2CH_2O), 3.82-3.93 (m, 3H, CH_2CH_2O and OCH_2), 3.98 (t, 2H, J = 6.3 Hz, OCH_2), 4.33 (d, 1H, J_{BA} = 14.4 Hz, CH_2O), 4.53 (d, 1H, J_{AB} = 14.4 Hz, J = 0.6 Hz, CH_2O), 4.71-4.75 (m, 1H, OCHO), 6.52 (d, 1H, J = 0.6 Hz, -C=CH-), 6.85-6.98 (m, 3H, Ar-H), 7.23-7.35 (m, 2H, Ar-H), 7.57 (s, 1H, -C=CH-).

2-Hydroxymethyl-5-(5-phenoxy-pentyloxy)-4*H*-pyran-4-one (EHT 1329).

EHT 6245 in MeOH and activated DOWEX (50WX8) were stirred 2 h at room temperature. The suspension was filtered and the precipitate was washed MeOH. After evaporation a viscuous yellow pale oil **EHT 1329** (80 % yield) was obtained.

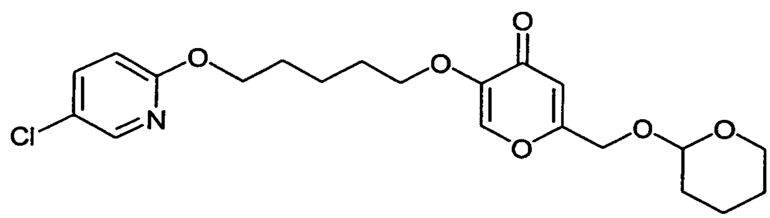


MW: 304.34; Yield: 80 %, Amber oil.

^{1}**H-NMR ($CDCl_3$, δ)**: 1.50-1.70 (m, 2H, CH_2), 1.75-1.99 (m, 4H, 2xCH_2), 2.78 (s broad, 1H, OH), 3.90 (t, J = 7.0 Hz, 2H, OCH_2), 3.99 (t, J = 7.0 Hz, 2H, OCH_2), 4.49 (d, J = 5.1 Hz, 2H, CH_2OH), 6.52 (d, J = 0.6 Hz, 1H, -C=CH-), 6.85-6.99 (m, 3H, Ar-H), 7.23-7.34 (m, 2H, Ar-H), 7.58 (s, 1H, -C=CH-).

5-[5-(5-Chloro-pyridin-2-yloxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0696).

The compound was prepared according to method A with 5-chloro-pyridin-2-ol (0.25 g, 1.93 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 a green oil **EHT 0696** (0.32 g, 39 % yield) was obtained.



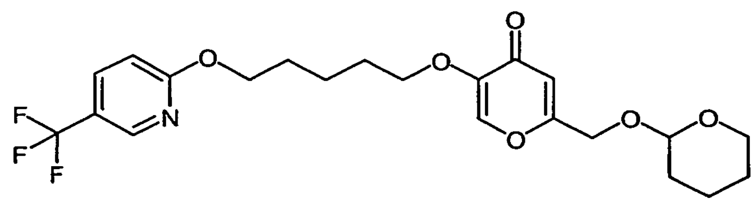
MW: 423.89; Yield 39%; Green oil.

^{1}**H-NMR ($CDCl_3$, δ)**: 1.45-1.92 (m, 12H, 6xCH_2), 3.50-3.58 (m, 1H, CH_2CH_2O), 3.82-3.97 (m, 3H, CH_2CH_2O and OCH_2), 3.98 (t, J = 6.3 Hz, 2H, OCH_2), 4.34 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.52 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.71-4.75 (m, 1H, OCHO), 6.52 (s, 1H, -C=CH-), 6.55 (d, J = 0.3 Hz, 1H, Pyr-H), 7.23-7.36 (m, 3H, Pyr-H), 7.58 (s, 1H, -C=CH-).

5-[5-(5-trifluoromethyl-pyridin-2-yloxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 1171).

The compound was prepared according to method A with 5-trifluoromethyl-pyridin-2-ol (0.25 g, 1.53 mmol). The organic layer was washed with NaOH 2N

then brine, dried over $MgSO_4$, filtered and evaporated to dryness. A green oil **EHT 1171** (0.54 g, 77 % yield) was obtained.

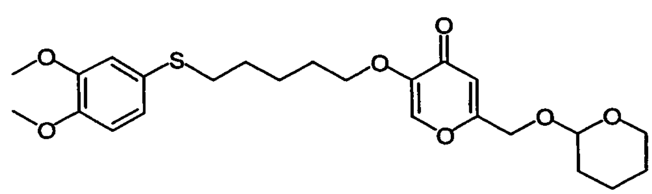


MW: 457.44; Yield 77 %; Green oil.

^{1}H-NMR ($CDCl_3$, δ): 1.45-1.95 (m, 12H, 6xCH_2), 3.50-3.58 (m, 1H, CH_2CH_2O), 3.82-3.95 (m, 5H, CH_2CH_2O and OCH_2), 3.99 (t, J = 7.5 Hz, 2H, OCH_2), 4.34 (d, J_{BA} = 14.4 Hz, 1H, CH_2O), 4.53 (d, J_{AB} = 14.4 Hz, 1H, CH_2O), 4.71-4.75 (m, 1H, OCHO), 6.52 (s, 1H, -C=CH-), 6.62 (d, J = 9.3 Hz, 1H, Pyr-H), 7.45 (dd, J = 9.3 Hz, J = 2.7 Hz, 1H, Pyr-H), 7.59 (s, 1H, -C=CH-), 7.70 (s, 1H, Pyr-H).

5-[5-(3,4-Dimethoxy-phenylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 3663).

The compound was prepared according to method A with 3,4-dimethoxy-benzenethiol (0.25 g, 1.47 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 a yellow oil **EHT 3663** (0.16 g, 23 % yield) was obtained.



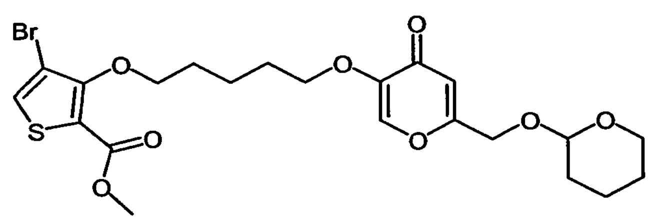
MW: 464.57; Yield 23 %; Yellow oil.

^{1}H-NMR ($CDCl_3$, δ): 1.47-1.95 (m, 12H, 6xCH_2), 2.87 (t, J = 7.2 Hz, 2H, -SCH_2), 3.50-3.58 (m, 1H, CH_2CH_2O), 3.75-3.95 (m, 3H, CH_2CH_2O and OCH_2), 3.88 (s, 6H, OMe), 4.33 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.52 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.71-4.75 (m, 1H, OCHO), 6.51 (d, J = 0.6 Hz, 1H, -

C=CH-), 6.81 (d, J = 8.1 Hz, 1H, Ar-H), 6.91-7.00 (m, 2H, Ar-H), 7.55 (s, 1H, -C=CH-).

4-Bromo-3-{5-[4-oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-thiophene-2-carboxylic acid methyl ester (EHT 4408).

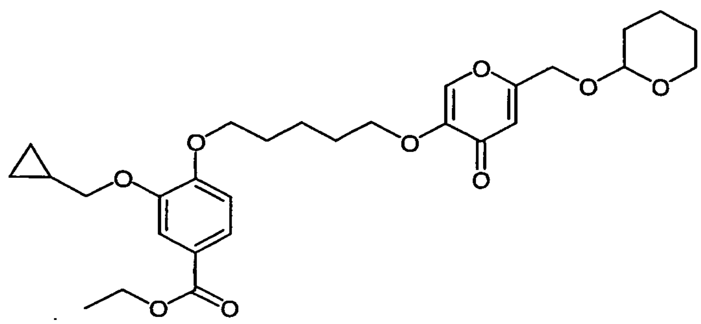
The compound was prepared according to method B with 4-bromo-3-hydroxy-thiophene-2-carboxylic acid methyl ester (0.25 g, 1.05 mmol). The organic layer was washed with NaOH 2N then brine, dried over $MgSO_4$, filtered and evaporated to dryness. An orange oil **EHT 4408** (0.17 g, 30 % yield) was obtained.



MW: 531.41; Yield: 30 %; Orange oil.
^{1}H-NMR (CD_3Cl, δ): 1.50-1.99 (m, 12H, 6xCH_2), 3.52-3.59 (m, 1H, CH_2O), 3.83-3.90 (m, 1H, CH_2O), 3.88 (s, 3H, MeO), 3.92 (t, J = 6.6 Hz, 2H, OCH_2O), 4.19 (t, J = 6.3 Hz, 2H, OCH_2O), 4.33 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, =CCH_2O), 4.52 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, =CCH_2O), 4.73 (m, 1H, OCH_2O), 6.51 (d, J = 0.6 Hz, 1H, –C=CH-), 7.39 (s, 1H, Ar-H), 7.59 (s, 1H, –C=CH-).

3-Cyclopropylmethoxy-4-{5-[4-oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-benzoic acid ethyl ester (EHT 7565).

The compound was prepared according to method B with 3-cyclopropylmethoxy-4-hydroxy-benzoic acid ethyl ester (0.25 g, 1.06 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 95:5 an orange oil **EHT 7565** (0.025 g, 4.5 % yield) was obtained.

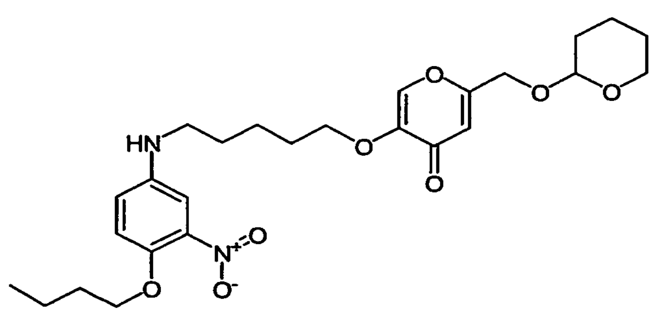


MW: 530.61; Yield: 4.5 %; Orange oil.

^{1}H-NMR ($CDCl_3$, δ): 0.35-0.40 (m, 2H, CH_2 cyclopropyl), 0.60-0.68 (m, 2H, CH_2 cyclopropyl), 1.27-1.35 (m, 1H, -CH- cyclopropyl),1.39 (t, J = 7.2 Hz, 3H, Me), 1.50-1.92 (m, 8H, $4xCH_2$), 1.92-2.10 (m, 4H, $2xCH_2$), 3.50-3.57 (m, 1H, CH_2O), 3.83-3.90 (m, 1H, CH_2O), 3.90 (d, J = 6.9 Hz, 2H, OCH_2 cyclopropyl), 3.92 (t, J = 6.6 Hz, 2H, OCH_2O), 4.10 (t, J = 6.3 Hz, 2H, OCH_2O), 4.34 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, $=CCH_2O$), 4.36 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.53 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, $=CCH_2O$), 4.70 (t, J = 3.0 Hz, 1H, OCH_2O), 6.52 (s, 1H, –C=CH-), 6.88 (d, J = 8.4 Hz, 1H, Ar-H), 7.56 (d, J = 1.8 Hz, 1H, Ar-H), 7.58 (s, 1H, –C=CH-), 7.66 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H, Ar-H).

5-[5-(4-Butoxy-3-nitro-phenylamino)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5230).

The compound was prepared according to method B with 4-butoxy-3-nitro-phenylamine (0.25 g, 1.19 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 95:5 a red dark oil **EHT 5230** (0.06 g, 10 % yield) was obtained.

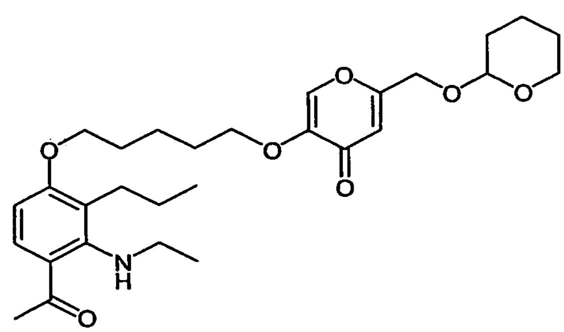


MW: 504.57; Yield: 10 %; Red dark oil.

^{1}H-NMR (CD_3Cl, δ): 0.99 (t, J = 7.2 Hz, 3H, Me), 1.40-2.00 (m, 16H, 8xCH_2), 3.25-3.32 (q broad, 2H, -NCH_2), 3.50-3.57 (m, 1H, CH_2O), 3.80-3.87 (m, 1H, CH_2O), 3.91 (t, J = 6.9 Hz, 2H, OCH_2), 3.92 (t, J = 6.3 Hz, 2H, OCH_2O), 3.95 (t, J = 6.3 Hz, 2H, OCH_2O), 4.35 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, =CCH_2O), 4.54 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, =CCH_2O), 4.73 (m, 1H, OCH_2O), 6.52 (s, 1H, –C=CH-), 6.83 (d, J = 9.3 Hz, 1H, Ar-H), 7.17 (dd, J = 9.3 Hz, J = 3.0 Hz, 1H, Ar-H), 7.58 (s, 1H, –C=CH-), 7.62 (d, J = 3.0 Hz, 1H, Ar-H), 8.00 (t broad, 1H, -NH).

5-[5-(4-Acetyl-3-ethylamino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9411).

The compound was prepared according to method A with 1-(2-ethylamino-4-hydroxy-3-propyl-phenyl)-ethanone (0.25 g, 1.13 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 a green oil **EHT 9411** (0.17 g, 29 % yield) was obtained.



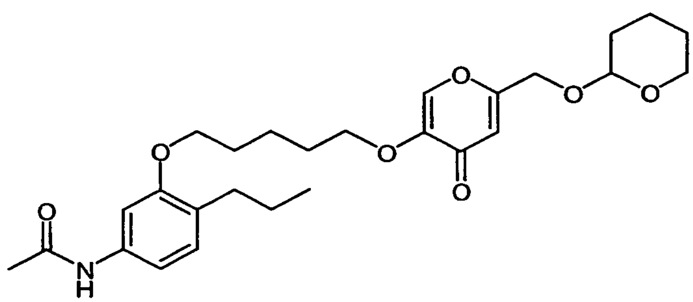
MW: 515.64; Yield: 29 %; Green oil.

^{1}H-NMR (CD_3Cl, δ): 0.99 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.23 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 1.49-1.99 (m, 14H, 7xCH_2), 2.57 (s, 3H, CH_3C=O), 2.58-2.65 (m, 2H, Ph-$CH_2CH_2CH_3$), 3.22 (q, J = 7.2 Hz, 2H, -NCH_2), 3.51-3.58 (m, 1H, CH_2O), 3.80-3.87 (m, 1H, CH_2O), 3.92 (t, J = 6.6 Hz, 2H, OCH_2), 4.04 (t, J = 6.3 Hz, 2H, OCH_2O), 4.34 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.53 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.73 (m, 1H, OCH_2O), 6.37 (d, J = 9.0 Hz, 1H, Ar-H), 6.52 (s, 1H,

–C=CH-), 7.58 (s, 1H, –C=CH-), 7.64 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.00 (s broad, 1H, NH).

<u>*N*-(3-{5-[4-Oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-4-propyl-phenyl)-acetamide (EHT 7151)</u>.

The compound was prepared according to method A with *N*-(3-hydroxy-4-propyl-phenyl)-acetamide (0.25 g, 1.29 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 a brown oil **EHT 7151** (0.21 g, 33 % yield) was obtained.



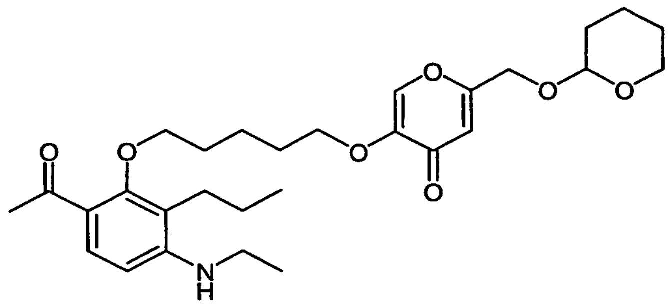
MW: 487.59; Yield: 33 %; Brown oil.

^{1}H-NMR (CD_3Cl, δ): 0.93 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.50-1.99 (m, 14H, 7xCH_2), 2.18 (s, 3H, CH_3C=O), 2.54 (t, *J* = 7.2 Hz, 2H, Ph-$CH_2CH_2CH_3$), 3.51-3.58 (m, 1H, CH_2O), 3.80-3.87 (m, 1H, CH_2O), 3.91 (t, *J* = 6.9 Hz, 2H, OCH_2), 3.95 (t, *J* = 6.3 Hz, 2H, OCH_2O), 4.35 (dd, J_{BA} = 14.4 Hz, *J* = 0.6 Hz, 1H, =CCH_2O), 4.54 (dd, J_{AB} = 14.4 Hz, *J* = 0.6 Hz, 1H, =CCH_2O), 4.74 (m, 1H, OCH_2O), 6.52 (s, 1H, –C=CH-), 6.91 (dd, *J* = 8.1 Hz, *J* = 1.8 Hz, 1H, Ar-H), 7.03 (d, 1H, *J* = 8.1 Hz,1H, Ar-H), 7.23 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.52 (s broad, 1H, NH), 7.60 (s, 1H, –C=CH-).

<u>5-[5-(6-Acetyl-3-ethylamino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7096)</u>.

The compound was prepared according to method A with 1-(4-ethylamino-2-hydroxy-3-propyl-phenyl)-ethanone (0.25 g, 1.12 mmol). After purification by

chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 an amber oil **EHT 7096** (0.06 g, 10 % yield) was obtained.

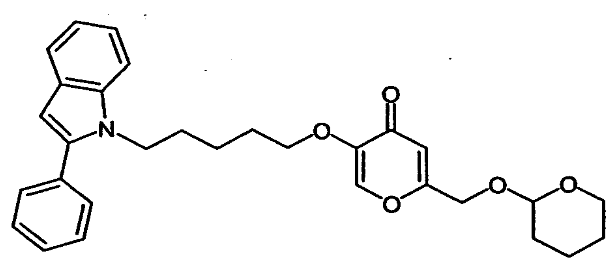


MW: 515.64; Yield: 10 %; Amber oil.

^{1}H-NMR (CD_3Cl, δ): 1.03 (t, J = 7.2 Hz, 3H, -CH_2CH_2*CH_3*), 1.32 (t, J = 7.2 Hz, 3H, NCH_2*CH_3*), 1.49-1.99 (m, 14H, 7xCH_2), 2.50-2.57 (m, 2H, Ph-*CH_2*CH_2CH_3), 2.57 (s, 3H, CH_3C=O), 3.25 (m, 2H, -NCH_2), 3.51-3.58 (m, 1H, CH_2O), 3.76 (t, J = 6.3 Hz, 2H, OCH_2O), 3.80-3.87 (m, 1H, CH_2O), 3.93 (t, J = 6.3 Hz, 2H, OCH_2), 4.00 (s broad, 1H -NH-), 4.34 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, =CCH_2O), 4.53 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, =CCH_2O), 4.74 (m, 1H, OCH_2O), 6.41 (d, J = 8.7 Hz, 1H, Ar-H), 6.52 (s, 1H, –C=CH-), 7.57 (d, J = 8.7 Hz, 1H, Ar-H), 7.60 (s, 1H, –C=CH-).

5-[5-(2-Phenyl-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9013).

The compound was prepared according to method B with 2-phenyl-1*H*-indole (0.25 g, 1.29 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 an amber oil **EHT 9013** (0.12 g, 19 % yield) was obtained.

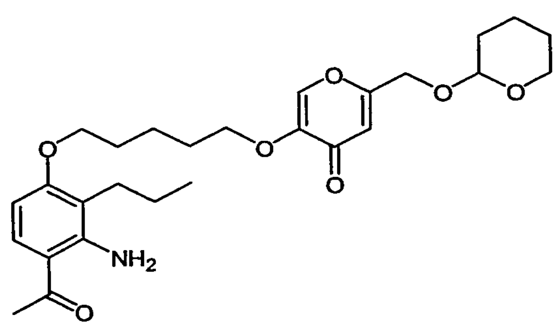


MW: 487.59; Yield: 19 %; Amber oil.

^{1}H-NMR ($CDCl_3$, δ): 1.25-1.40 (m, 2H, CH_2), 1.53-2.00 (m, 10H, 5xCH_2), 3.52-3.60 (m, 1H, CH_2CH_2O), 3.73 (t, 2H, J = 6.3 Hz, -NCH_2), 3.82-3.96 (m, 1H, CH_2CH_2O), 4.20 (t, J = 6.6 Hz, 2H, OCH_2), 4.34 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.53 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.72-4.77 (m, 1H, OCHO), 6.51 (d, J = 0.6 Hz, 1H, -C=CH-), 6.53 (d, J = 0.9 Hz, 1H, Ind-H), 7.15 (m, 1H, Ind-H), 7.25 (m, 1H, Ind-H), 7.30-7.50 (m, 7H, Ph-H, Ind-H & -C=CH-), 7.64 (d, J = 7.8 Hz, 1H, Ind-H).

5-[5-(4-Acetyl-3-amino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-*4H*-pyran-4-one (EHT 5769).

The compound was prepared according to method A with 1-(2-amino-4-hydroxy-3-propyl-phenyl)-ethanone (0.25 g, 1.29 mmol). After purification by chromatography on silica using as eluent heptane:AcOEt = 7:3 a yellow oil **EHT 5769** (0.115 g, 18 % yield) was obtained.



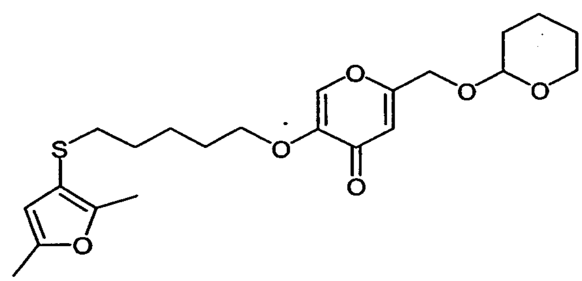
MW: 487.59; Yield: 18 %; Yellow oil.

^{1}H-NMR (CD_3Cl, δ): 0.98 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.49-1.99 (m, 14H, 7xCH_2), 2.55 (t, J = 7.2 Hz, 2H, Ph-$CH_2CH_2CH_3$), 2.57 (s, 3H, CH_3C=O), 3.51-3.58 (m, 1H, CH_2O), 3.80-3.87 (m, 1H, CH_2O), 3.92 (t, J = 6.3 Hz, 2H, OCH_2O), 4.04 (t, J = 6.3 Hz, 2H, OCH_2), 4.34 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.53 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.74 (m, 1H, OCH_2O), 6.27 (d, J = 9.0 Hz, 1H, Ph-H),

6.52 (s broad, 3H, –C=CH- and -NH_2), 7.58 (s, 1H, –C=CH-), 7.63 (d, J = 9.0 Hz, 1H, Ph-H).

5-[5-(2,5-Dimethyl-furan-3-ylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7976).

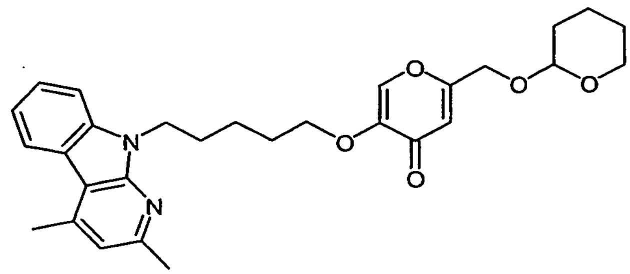
The compound was prepared according to method A with 2,5-dimethyl-furan-3-thiol (0.25 g, 1.95 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 a yellow oil **EHT 7976** (0.13 g, 16 % yield) was obtained.



MW: 422.54; Yield: 16 %; Yellow oil.
^{1}H-NMR (CD_3Cl, δ): 1.49-1.99 (m, 12H, 6xCH_2), 2.24 (s, 3H, Me), 2,30 (s, 3H, Me), 2.61 (t, J = 6.9 Hz, 2H, CH_2S), 3.51-3.58 (m, 1H, CH_2O), 3.80-3.87 (m, 1H, CH_2O), 3.89 (t, J = 6.3 Hz, 2H, OCH_2O), 4.34 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.53 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.74 (t, J = 3.0 Hz, 1H, OCH_2O), 5.92 (s, 1H, Ar-H), 6.51 (s 1H, –C=CH-), 7.27 (s, 1H, Ar-H), 7.56 (s, 1H, –C=CH-).

5-[5-(2,4-Dimethyl-pyrido[2,3-*b*]indol-9-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6448).

The compound was prepared according to method A with 2,4-dimethyl-9*H*-pyrido[2,3-*b*]indole (0.25 g, 1.27 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 99:1 an amber oil **EHT 6448** (0.22 g, 35 % yield) was obtained.

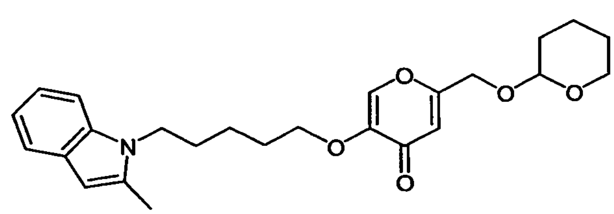


MW: 490.59, Yield: 35 %; Amber oil.

^{1}H-NMR ($CDCl_3$, δ): 1.49-1.99 (m, 12H, 6xCH_2), 2.54 (s, 3H, Me), 2,67 (s, 3H, Me), 3.21 (t, J = 6.6 Hz, 2H, CH_2N), 3.45 (t, J = 6.3 Hz, 2H, OCH_2O), 3.50-3.58 (m, 1H, CH_2O), 3.82-3.89 (m, 1H, CH_2O), 4.23 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.41 (d, J_{AB} = 16.8 Hz, 1H, =CCH_2O), 4.77 (m, 1H, OCH_2O), 6.47 (s 1H, –C=CH-), 6.97 (s, 1H, Ar-H), 7.38 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H, Ar-H), 7.51 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H, Ar-H), 7.70 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H, Ar-H), 8.07 (d, J = 7.5 Hz, 1H, Ar-H), 8.17 (s, 1H, –C=CH-).

5-[5-(2-Methyl-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2427).

The compound was prepared according to method A with 2-methyl-1*H*-indole (0.25 g, 1.90 mmol). After purification by chromatography on silica using as eluent toluene:MeOH = 99:1 a green oil **EHT 2427** (0.015 g, 2 % yield) was obtained.



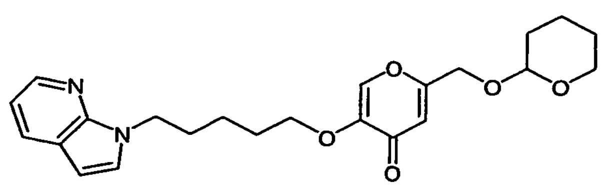
MW: 425.52, Yield: 2 %; Green oil.

^{1}H-NMR ($CDCl_3$, δ): 1.39-1.99 (m, 12H, 6xCH_2), 2.45 (s, 3H, Me), 3.23 (t, J = 6.6 Hz, 2H, CH_2N), 3.30 (t, J = 6.3 Hz, 2H, OCH_2O), 3.50-3.58 (m, 1H, CH_2O), 3.82-3.89 (m, 1H, CH_2O), 4.22 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.41 (d, J_{AB} = 16.8

Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.42 (d, J = 1.8 Hz, 1H, Ind-H), 6.45 (s 1H, –C=CH-), 7.10-7.28 (m, 2H, Ar-H), 7.34 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H, Ind-H), 7.51 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H, Ind-H), 7.70 (dd, J = 7.5 Hz, J = 0.6 Hz, 1H, Ind-H), 7.47 (s, 1H, –C=CH-), 7.51 (d, J = 1.8 Hz, 1H, Ind-H).

5-(5-Pyrrolo[2,3-*b*]pyridin-1-yl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8309).

The compound was prepared according to method A with 1*H*-Pyrrolo[2,3-*b*]pyridine (0.25 g, 2.11 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 99:1 a brown solid **EHT 8309** (0.04 g, 5 % yield) was obtained.



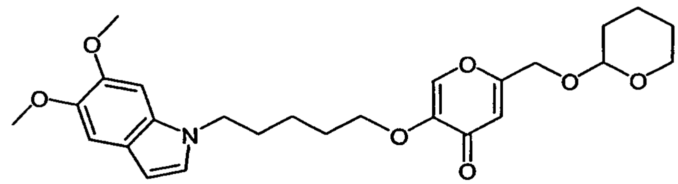
MW: 412.49 Yield: 5 %; Brown solid; Mp = 37.9 °C.

^{1}H-NMR (CD_3Cl, δ): 1.41-2.02 (m, 12H, 6xCH_2), 3.46 (t, J = 6.6 Hz, 2H, CH_2N), 3.51-3.59 (m, 1H, CH_2O), 3.87 (t, J = 6.6 Hz, 2H, OCH_2O), 3.88-3.95 (m, 1H, CH_2O), 4.19 (d, J_{BA} = 16.5 Hz, 1H, =CCH_2O), 4.38 (d, J_{AB} = 16.5 Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.31 (s 1H, –C=CH-), 6.70 (d, J = 3.6 Hz, 1H, Ar-H), 7.22 (dd, J = 7.8 Hz, J = 4.8 Hz, 1H, Ar-H), 7.93 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H, Ar-H), 8.17 (d, J = 3.6 Hz, 1H, Ar-H), 7.51 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H, Ar-H), 8.42 (s, 1H, –C=CH-).

5-[5-(5,6-Dimethoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5457).

The compound was prepared according to method A with 5,6-dimethoxy-1*H*-indole (0.25 g, 1.41 mmol). After purification by chromatography on silica using

as eluent CH_2Cl_2:MeOH = 99:1 a yellow oil **EHT 5457** (0.12 g, 18 % yield) was obtained.

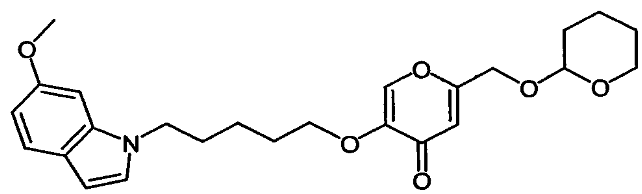


MW: 471.54, Yield: 18 %; Yellow oil.

^{1}H-NMR (CD_3Cl, δ): 1.49-2.01 (m, 12H, 6xCH_2), 3.45 (t, J = 6.6 Hz, 2H, CH_2N), 3.51-3.59 (m, 1H, CH_2O), 3.80 (t, J = 6.6 Hz, 2H, OCH_2O), 3.83-3.91 (m, 1H, CH_2O), 3.95 (s, 3H, OMe), 4.00 (s, 3H, OMe), 4.09 (d, J_{BA} = 18.9 Hz, 1H, =CCH_2O), 4.30 (d, J_{AB} = 18.9 Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.33 (s 1H, –C=CH-), 6.65 (d, J = 3.6 Hz, 1H, Ind-H), 7.03 (s, 1H, Ind-H), 7.08 (s, 1H, Ind-H), 7.76 (s, 1H, –C=CH-), 7.89 (d, J = 3.6 Hz, 1H, Ind-H).

5-[5-(6-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5235).

The compound was prepared according to method A with 6-methoxy-1*H*-indole (0.25 g, 1.70 mmol). After purification by chromatography on silica using as eluent toluene a yellow solid **EHT 5235** (0.045 g, 6 % yield) was obtained.



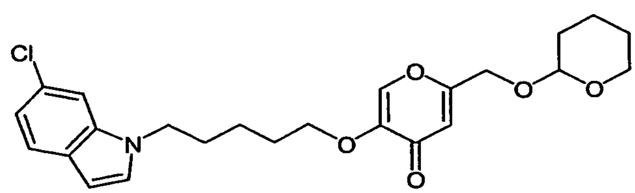
MW: 441.52; Yield: 6 %; Yellow solid, Mp = 37.8 °C.

^{1}H-NMR (CD_3Cl, δ): 1.49-2.01 (m, 12H, 6xCH_2), 3.45 (t, J = 6.6 Hz, 2H, CH_2N), 3.51-3.59 (m, 1H, CH_2O), 3.80 (t, J = 6.6 Hz, 2H, OCH_2O), 3.83-3.91 (m, 1H,

CH_2O), 3.92 (s, 3H, OMe), 4.20 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.40 (d, J_{AB} = 16.8 Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.33 (s 1H, –C=CH-), 6.67 (d, J = 3.6 Hz, 1H, Ind-H), 6.90 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H, Ind-H), 7.02 (d, J = 2.1 Hz, 1H, Ind-H), 7.49 (d, J = 8.7 Hz, 1H, Ind-H), 7.79 (s, 1H, –C=CH-), 7.89 (d, J = 3.6 Hz, 1H, Ind-H).

5-[5-(6-Chloro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8617).

The compound was prepared according to method A with 6-chloro-1*H*-indole (0.25 g, 1.65 mmol). After purification by chromatography on silica using as eluent toluene a yellow solid **EHT 8617** (0.007 g, 1 % yield) was obtained.

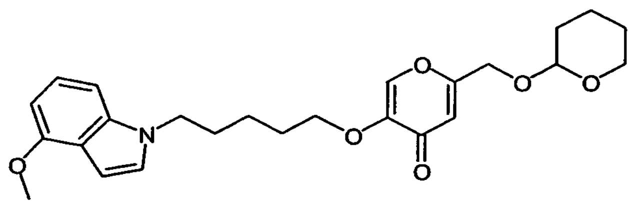


MW: 445.94, Yield: 1 %; Yellow solid.

^{1}H-NMR (CD_3Cl, δ): 1.50-2.00 (m, 12H, 6xCH_2), 3.44 (t, J = 6.6 Hz, 2H, CH_2N), 3.52-3.60 (m, 1H, CH_2O), 3.80 (t, J = 6.6 Hz, 2H, OCH_2O), 3.83-3.91 (m, 1H, CH_2O), 4.20 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.40 (d, J_{AB} = 16.8 Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.33 (s 1H, –C=CH-), 6.72 (d, J = 3.6 Hz, 1H, Ind-H), 7.15-7.27 (m, 2H, Ind-H), 7.54 (d, J = 8.4 Hz, 1H, Ind-H), 7.72 (s, 1H, –C=CH-), 7.99 (d, J = 3.6 Hz, 1H, Ind-H).

5-[5-(4-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0091).

The compound was prepared according to method A with 4-methoxy-1*H*-indole (0.25 g, 1.70 mmol). After purification by chromatography on silica using as eluent toluene a yellow solid **EHT 0091** (0.08 g, 11 % yield) was obtained.



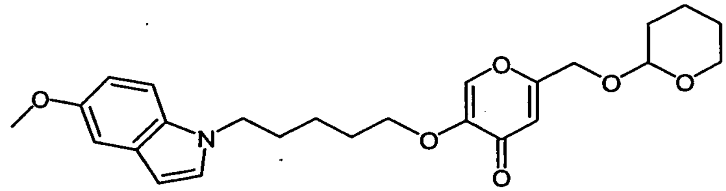
MW: 441.52, Yield: 11 %; Yellow solid, Mp = 113.3 °C.

^{1}H-NMR ($CDCl_3$, δ): 1.50-2.00 (m, 12H, $6xCH_2$), 3.44 (t, J = 6.6 Hz, 2H, CH_2N), 3.52-3.60 (m, 1H, CH_2O), 3.80 (t, J = 6.6 Hz, 2H, OCH_2O), 3.83-3.91 (m, 1H, CH_2O), 3.98 (s, 3H, OMe), 4.19 (d, J_{BA} = 16.8 Hz, 1H, $=CCH_2O$), 4.39 (d, J_{AB} = 16.8 Hz, 1H, $=CCH_2O$), 4.75 (m, 1H, OCH_2O), 6.32 (s 1H, –C=CH-), 6.68 (d, J = 7.2 Hz, 1H, Ind-H), 6.86 (d, J = 3.6 Hz, 1H, Ind-H), 7.18 (d, J = 8.4 Hz, 1H, Ind-H), 7.25 (m, 1H, Ind-H), 7.82 (s, 1H, –C=CH-), 7.92 (d, J = 3.6 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 443.9 ($[MH]^+$+1, 100), 441.9 ($[MH]^+$, 70).

5-[5-(5-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8140).

The compound was prepared according to method A with 5-methoxy-1*H*-indole (0.25 g, 1.70 mmol). After purification by chromatography on silica using as eluent toluene a yellow oil **EHT 8140** (0.075 g, 10 % yield) was obtained.

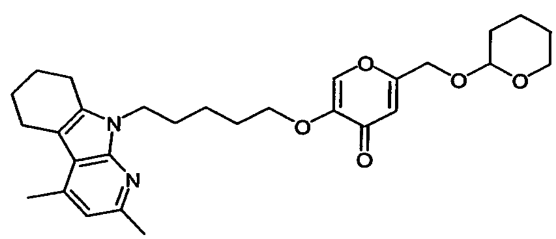


MW: 441.52, Yield: 10 %; Yellow oil.

^{1}H-NMR ($CDCl_3$, δ): 1.48-2.00 (m, 12H, 6xCH_2), 3.45 (t, *J* = 6.6 Hz, 2H, CH_2N), 3.51-3.59 (m, 1H, CH_2O), 3.80 (t, *J* = 6.6 Hz, 2H, OCH_2O), 3.83-3.91 (m, 1H, CH_2O), 3.88 (s, 3H, OMe), 4.19 (d, J_{BA} = 16.5 Hz, 1H, =CCH_2O), 4.39 (d, J_{AB} = 16.5 Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.30 (s 1H, –C=CH-), 6.69 (d, *J* = 3.6 Hz, 1H, Ind-H), 6.97 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1H, Ind-H), 7.10 (d, *J* = 2.4 Hz, 1H, Ind-H), 7.45 (d, *J* = 9.0 Hz, 1H, Ind-H), 7.80 (s, 1H, –C=CH-), 7.99 (d, *J* = 3.6 Hz, 1H, Ind-H).

5-[5-(2,4-Dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-*b*]indol-9-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7337).

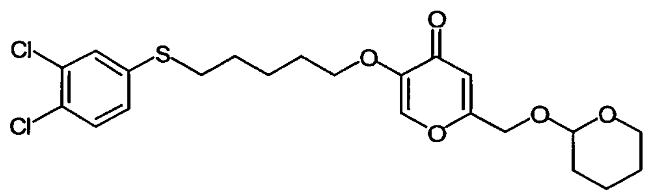
The compound was prepared according to method A with 2,4-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indole (0.25 g, 1.25 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 99:1 a yellow oil **EHT 7337** (0.03 g, 5 % yield) was obtained.



MW: 494.28, Yield: 5 %; Yellow oil.
^{1}H-NMR ($CDCl_3$, δ): 1.48-2.00 (m, 16H, 8xCH_2), 2.57 (s, 3H, Me), 2.59 (s, 3H, Me), 2.71-2.77 (m, 2H, CH_2C=C), 2.91-2.97 (m, 2H, CH_2C=C), 3.32 (t, *J* = 6.6 Hz, 2H, CH_2N), 3.51-3.59 (m, 1H, CH_2O), 3.56 (t, *J* = 6.6 Hz, 2H, OCH_2O), 3.83-3.91 (m, 1H, CH_2O), 3.88 (s, 3H, OMe), 4.19 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.37 (d, J_{AB} = 16.8 Hz, 1H, =CCH_2O), 4.73 (m, 1H, OCH_2O), 6.37 (s 1H, –C=CH-), 6.73 (s, 1H, Ar-H), 7.80 (s, 1H, –C=CH-).

<u>5-[5-(3,4-Dichloro-phenylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0407).</u>

The compound was prepared according to method A with 3,4-dichloro-benzenethiol (0.25 g, 1.40 mmol). The organic layer was washed with NaOH 2N then brine, dried over $MgSO_4$, filtered and evaporated to dryness. A white oil **EHT 0407** (0.41 g, 62 % yield) was obtained.



MW: 473.41; Yield 62 %; White oil.

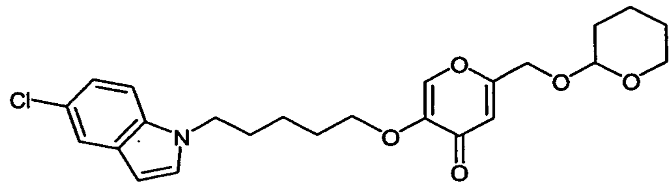
^{1}H-NMR ($CDCl_3$, δ): 1.47-1.95 (m, 12H, 6xCH_2), 2.93 (t, J = 7.2 Hz, 2H, SCH_2), 3.50-3.58 (m, 1H, CH_2CH_2O), 3.80-3.88 (m, 1H, CH_2CH_2O), 3.86 (t, J = 7.2 Hz, 2H, OCH_2), 4.36 (dd, J_{BA} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.52 (dd, J_{AB} = 14.4 Hz, J = 0.6 Hz, 1H, CH_2O), 4.72 (t, J = 3.0 Hz, 1H, OCHO), 6.51 (d, J = 0.6 Hz, 1H, -C=CH-), 7.12 (dd, J = 8.4, J = 2.1, Hz, 1H, Ar-H), 7.29-7.40 (m, 2H, Ar-H), 7.56 (s, 1H, -C=CH-).

MS-ESI *m/z* (rel. int.): 473, 475, 477 ($[MH]^+$, 65, 45, 8), 247,249, 251 (100, 68, 11).

HPLC: Method A, detection UV 254 nm, EHT 0407 RT = 7.51 min, peak area 93.9%.

<u>5-[5-(5-Chloro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0823).</u>

The compound was prepared according to method A with 5-chloro-1*H*-indole (0.25 g, 1.65 mmol). After purification by chromatography on silica using as eluent heptane:AcOEt = 9:1 a yellow solid **EHT 0823** (0.06 g, 8 % yield) was obtained.

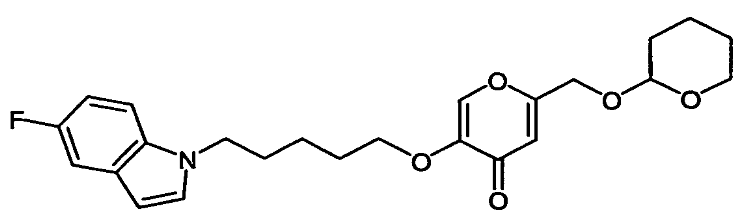


MW: 445.94, Yield: 8 %; Yellow solid.

^{1}H-NMR ($CDCl_3$, δ): 1.39-1.99 (m, 12H, 6xCH_2), 3.44 (t, J = 6.6 Hz, 2H, CH_2N), 3.50-3.58 (m, 1H, CH_2O), 3.80 (t, J = 6.6 Hz, 2H, OCH_2O), 3.87-3.95 (m, 1H, CH_2O), 4.20 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.39 (d, J_{AB} = 16.8 Hz, 1H, =CCH_2O), 4.75 (m, 1H, OCH_2O), 6.32 (s 1H, –C=CH-), 6.69 (d, J = 3.3 Hz, 1H, Ind-H), 7.29 (dd, J = 9.0 Hz, J = 3.6 Hz 1H, Ind-H), 7.47 (d, J = 9.0 Hz, 1H, Ind-H), 7.61 (d, J = 3.6 Hz, 1H, Ind-H), 7.76 (s, 1H, –C=CH-), 7.51 (d, J = 3.3 Hz, 1H, Ind-H).

5-[5-(5-Fluoro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0533).

The compound was prepared according to method A with 5-fluoro-1*H*-indole (0.25 g, 1.85 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 99:1 a yellow solid **EHT 0533** (0.07 g, 9 % yield) was obtained.



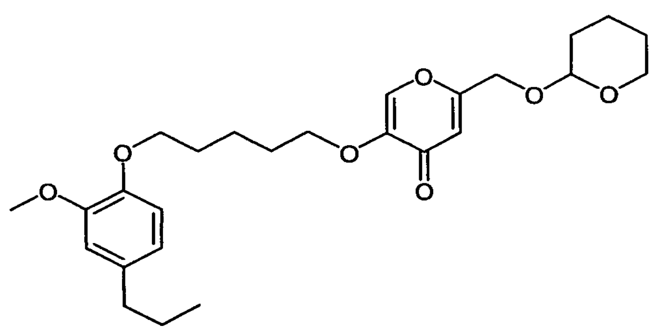
MW: 429.48, Yield: 9 %; Yellow solid; Mp = 72.1 °C.

^{1}H-NMR ($CDCl_3$, δ): 1.45-1.99 (m, 12H, 6xCH_2), 3.45 (t, J = 6.6 Hz, 2H, CH_2N), 3.50-3.58 (m, 1H, CH_2O), 3.80 (t, J = 6.6 Hz, 2H, OCH_2O), 3.87-3.95 (m, 1H, CH_2O), 4.20 (d, J_{BA} = 16.8 Hz, 1H, =CCH_2O), 4.38 (d, J_{AB} = 16.8 Hz, 1H,

=CCH_2O), 4.75 (m, 1H, OCH_2O), 6.32 (s, 1H, –C=CH-), 6.71 (d, J = 3.6 Hz, 1H, Ind-H), 7.07 (ddd, J = 9.0 Hz, J = 3.6 Hz 1H, Ind-H), 7.29 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H, Ind-H), 7.47 (m, 1H, Ind-H), 7.78 (s, 1H, –C=CH-), 8.06 (d, J = 3.6 Hz, 1H, Ind-H).

5-[5-(2-Methoxy-4-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9387).

The compound was prepared according to method A with 2-methoxy-4-propyl-phenol (0.25 g, 1.50 mmol). After purification by chromatography on silica using as eluent CH_2Cl_2:MeOH = 98:2 a brown oil **EHT 9387**(0.065 g, 9 % yield) was obtained.



MW: 460.56, Yield: 9 %; Brown oil.

^{1}H-NMR ($CDCl_3$, δ): 0.95 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.50-1.99 (m, 14H, 7xCH_2), 2.54 (t, J = 17.9 Hz, 2H, $CH_2CH_2CH_3$), 3.50-3.58 (m, 1H, CH_2O), 3.84-3.93 (m, 1H, CH_2O), 3.86 (s, 3H, OMe), 3.90 (t, J = 6.6 Hz, 2H, CH_2O), 4.01 (t, J = 6.6 Hz, 2H, CH_2O), 4.34 (d, J_{BA} = 14.4 Hz, 1H, C=CCH_2O), 4.53 (d, J_{AB} = 14.4 Hz, 1H, C=CCH_2O), 4.74 (m, 1H, OCH_2O), 6.51 (s, 1H, –C=CH-), 6.65-6.86 (m, 3H, Ar-H), 7.57 (s, 1H, –C=CH-).

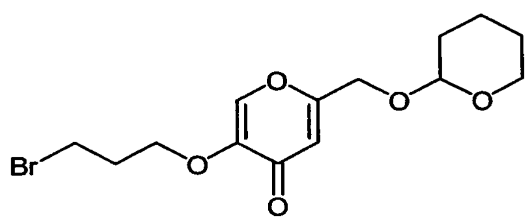
Synthesis of Derivatives EHT 4283, EHT 5741, EHT 3089, EHT 6895, EHT 6353, EHT 2358, EHT 8733 and EHT 2271.

General procedure for O-alkylation of 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4H-pyran-4-one to obtain intermediates 11, 12, 13, 14, 15, 16 and 17:

5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.0 eq) was charged in a sealed tube. Anhydrous DMF (25 mL) and Cs_2CO_3 (1.1 eq) were successively added. After 5-10 min, the dibromoalkane (3.0-5.0 eq) was added *via* syringe. The sealed tube was heated at 50-80°C for 2 h 30. After cooling and filtration, DMF was removed *in vacuo*, the crude oil was purified by chromatography on silica using as eluent AcOEt:CH_2Cl_2 = 20:80.

5-(3-Bromo-propoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 11.

The compound was prepared according to the above general procedure using 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol), Cs_2CO_3 (1.58 g, 4.86 mmol) and 1,3-dibromopropane (2.25 mL, 22.1 mmol). The sealed tube was heated at 50°C for 2 h 30. A colorless oil **11** was obtained (1.01 g, 66 % yield).

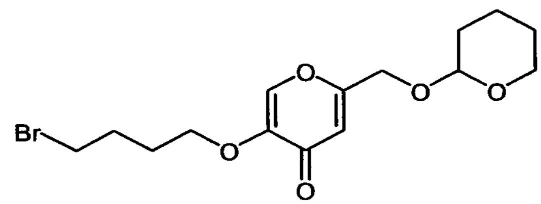


MW: 347.20; Yield: 66 %, Colorless oil.

^{1}H-NMR ($CDCl_3$, δ): 1.49-1.91 (m, 6H, 3xCH_2), 2.29-2.40 (m, 2H, CH_2), 3.50-3.59 (m, 1H, OCH_2), 3.61 (t, J = 6.2 Hz, 2H, $BrCH_2$), 3.78-3.88 (m, 1H, OCH_2), 4.03 (t, J = 5.8 Hz, 2H, OCH_2), 4.32 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.52 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.69-4.74 (m, 1H, OC*H*O), 6.51 (s, 1H, -C=CH-), 7.63 (s, 1H, -C=CH-).

5-(4-Bromo-butoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 12.

The compound was prepared according to the above general procedure using 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol), Cs_2CO_3 (1.58 g, 4.86 mmol) and 1,4-dibromobutane (2.00 mL, 16.7 mmol). The sealed tube was heated at 80°C for 2 h 30. A white solid **12** was obtained (1.14 g, 71 % yield).

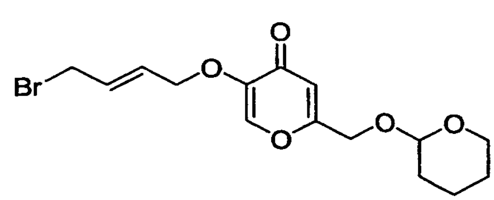


MW: 361.23; Yield: 71 %, White solid, Mp = 71.5 °C.

^{1}H-NMR ($CDCl_3$, δ): 1.49-1.91 (m, 6H, $3xCH_2$), 1.91-2.10 (m, 4H, $2xCH_2$), 3.48 (t, J = 6.5 Hz, 2H, $BrCH_2$), 3.50-3.59 (m, 1H, OCH_2), 3.76-3.88 (m, 1H, OCH_2), 3.92 (t, J = 6.1 Hz, 2H, OCH_2), 4.32 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.51 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.70-4.75 (m, 1H, OC*H*O), 6.50 (s, 1H, -C=CH-), 7.58 (s, 1H, -C=CH-).

<u>(*E*)-5-(4-Bromo-but-2-enyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **13.**</u>

The compound was prepared according to the above general procedure using 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol), Cs_2CO_3 (1.58 g, 4.86 mmol) and 1,4-dibromo-but-2-ene (1.89 g, 8.84 mmol). The sealed tube was heated at 60°C for 2 h. An oil **13** was obtained (190 mg, 12 % yield).

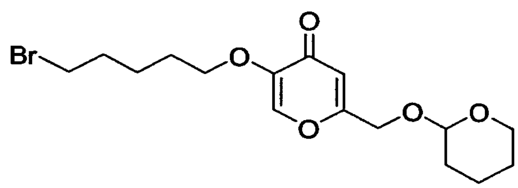


MW: 359.21; Yield: 12%, Oil.

^{1}H-NMR ($CDCl_3$, δ): 1.35-1.90 (m, 14H, 7xCH_2), 3.64-3.70 (m, 2H, OCH_2), 3.78-3.84 (m, 1H, OCH_2), 4.32 (d, J_{BA} = 14.4 Hz, 1H, OCH_2), 4.51 (d, J_{AB} = 14.4 Hz, 1H, OCH_2), 4.53 (m, 1H, OCHO), 4.66-4.75 (m, 2H, $BrCH_2$), 5.97 (m, 2H, -CH=CH-), 6.51 (s, 1H, -C=CH-), 7.60 (s, 1H, -C=CH-).

5-(5-Bromo-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 14.

The compound was prepared according to the above general procedure using 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (3.5 g, 15.5 mmol) in 20 mL of DMF, Cs_2CO_3 (5.04 g, 15.5 mmol) and 1,5-dibromopentane (8.8 g, 36.7 mmol). The sealed tube was heated at 90-95 °C for 1 h 40. A white solid **14** was obtained (5.30 g, 91 % yield).



MW: 375.25; Yield: 91 %; Yellow solid; Mp: 140.3 °C.

R*f*: 0.36 (CH_2Cl_2:ethyl acetate = 8:2).

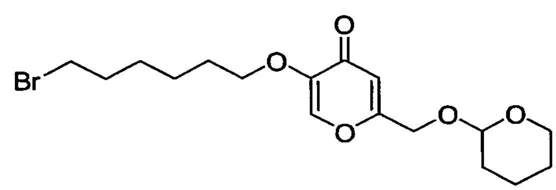
^{1}H-NMR ($CDCl_3$, δ): 1.53-1.84 (m, 12H, 6xCH_2), 3.52-3.57 (m, 1H, OCH_2), 3.77-3.84 (m, 1H, O-CH_2), 4.30 (d, J_{BA} = 14.5 Hz, 1H, OCH_2), 4.48 (s, 2H, OCH_2), 4.50 (d, J_{AB} = 14.5 Hz, 1H, OCH_2), 4.70 (t, J = 3.1 Hz, 1H, OCHO), 5.07 (s, 2H, $BrCH_2$), 6.51 (s, 1H, -C=CH-), 7.36-7.42 (m, 4H, Ar-H), 7.53 (s, 1H, -C=CH-).

MS-ESI *m/z* (rel. int.): 374.9-376.9 ([MH]$^+$, 100).

HPLC: Method A, Detection UV 254 nm, RT= 5.73 min.

5-(5-Bromo-hexyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 15.

5-Hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.50 g, 6.60 mmol) was charged in a 30 mL sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (10 mL), Cs_2CO_3 (2.30 g, 7.00 mmol) and 1,6-dibromo-hexane (3.20 g, 13.30 mmol) were successively added. The reaction mixture was stirred 2 h at 60°C. After evaporation of DMF, the crude compound was purified by column chromatography (SiO_2, CH_2Cl_2:AcOEt = 8:2) to give after evaporation 5-(6-bromo-hexyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **15** as an oil (190 mg, 52 % yield).



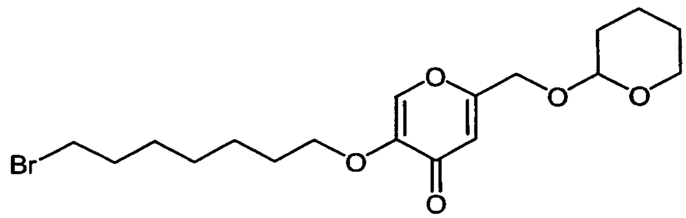
MW: 389.28; Yield: 52%; Oil.

^{1}H-NMR ($CDCl_3$, δ): 1.40-1.95 (m, 14H, 7xCH_2), 3.45 (t, J = 6.7 Hz, 2H, $BrCH_2$), 3.52-3.64 (m, 1H, OCH_2), 3.82-3.92 (m, 1H, OCH_2), 3.90 (t, J = 6.5 Hz, 2H, OCH_2), 4.36 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.56 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.74-4.79 (m, 1H, OC*H*O), 6.54 (s, 1H, -C=CH-), 7.60 (s, 1H, -C=CH-).

MS-ESI *m/z* (rel. int.): 389-391 ([MH]$^+$, 97-100).

<u>5-(7-Bromo-heptyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 16.</u>

The compound was prepared according to the above general procedure using 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol), Cs_2CO_3 (1.58 g, 4.86 mmol) and 1,7-dibromoheptane (2.5 mL, 14.6 mmol). The sealed tube was heated at 80°C for 2 h 30. A white solid **16** was obtained (1.40 g, 78 % yield).

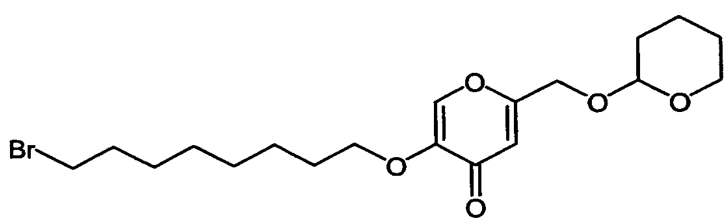


MW: 403.31; Yield: 78 %, White solid.

^{1}H-NMR ($CDCl_3$, δ): 1.25-1.92 (m, 16H, 8xCH_2), 3.40 (t, J = 6.8 Hz, 2H, BrCH_2), 3.50-3.59 (m, 1H, OCH_2), 3.78-3.88 (m, 1H, OCH_2), 3.85 (t, J = 6.6 Hz, 2H, OCH_2), 4.32 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.51 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.70-4.75 (m, 1H, OC*H*O), 6.50 (s, 1H, -C=CH-), 7.55 (s, 1H, -C=CH-).

5-(8-Bromo-octyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 17.

The compound was prepared according to the above general procedure using 5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol), Cs_2CO_3 (1.58 g, 4.86 mmol) and 1,8-dibromooctane (4.12 mL, 22.1 mmol). The sealed tube was heated at 80°C for 2 h 30. A white solid **17** was obtained (1.40 g, 78 % yield).



MW: 417.33; Yield: 62 %; Yellow oil.

^{1}H-NMR ($CDCl_3$, δ): 1.25-1.92 (m, 18H, 9xCH_2), 3.40 (t, J = 6.8 Hz, 2H, BrCH_2), 3.50-3.59 (m, 1H, OCH_2), 3.78-3.88 (m, 1H, OCH_2), 3.85 (t, J = 6.6 Hz, 2H, OCH_2), 4.32 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.51 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.70-4.75 (m, 1H, OC*H*O), 6.50 (s, 1H, -C=CH-), 7.55 (s, 1H, -C=CH-).

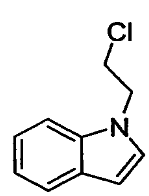
__General procedure for substitution of bromoalkyl kojic acid OTHP derivatives by indole:__

NaH 60% dispersion in oil (1.3 eq) was charged in a 25 mL three necked round bottom flask equipped with a condenser and under a nitrogen atmosphere. Indole (1.3 eq) and DMSO (4 mL) were added. The mixture was heated at 60°C for 2h. After cooling the brominated derivative (1.0 eq) was added. The reaction mixture became red dark and went to red brown light. After 3 h at 60°C the reaction mixture was cooled. CH_2Cl_2 was added (20 mL) and the solution was washed with water (4 X 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by chromatography on silica using as eluent AcOEt:CH_2Cl_2 = 20/80.

__Synthesis of intermediates 18.__

__1-(2-Chloro-ethyl)-1*H*-indole 18.__

To a solution of indole (1.00 g, 8.5 mmol) in dichloroethane (8.6 g, 85.0 mmol) were added KOH (1.2 g, 17.0 mmol) in 5 mL of H_2O and TBAF 1M in THF (8 mL, 8.0 mmol). The reaction mixture was vigorously stirred at 70-90 °C for 15 h. After cooling the reaction mixture was extracted with dichloromethane (3 x 50 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by column chromatography in cyclohexane:ethyl acetate = 98:2 to 95:5. After evaporation a pasty product 1-(2-chloro-ethyl)-1*H*-indole **18** (0.27 g, 18% yield) was obtained.



MW: 179.65; Yield: 18 %; Colorless oil.

***R**f*: 0.65 (Cyclohexane:Ethyl Acetate = 8:2).

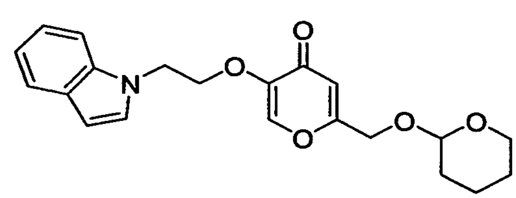
^{1}H-NMR ($CDCl_3$, δ): 3.71 (t, J = 6.6 Hz, NCH_2), 4.36 (t, J = 6.6 Hz, $ClCH_2$), 6.45 (dd, J = 3.2 Hz, J = 0.8 Hz, 1H, Ind-H), 7.03-7.08 (m, 2H, Ind-H), 7.15 (ddd, J = 8.2 Hz, J = 7.0 Hz, J = 1.1 Hz, 1H, Ind-H), 7.25 (dd, J = 8.1 Hz, J = 0.8 Hz, 1H, Ind-H), 7.57 (td, J = 7.8 Hz, J = 0.9 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 180.0-182.0 ($[MH]^+$, 100).

HPLC: Method A, Detection UV 254 nm, RT= 6.15 min.

5-[2-Indol-1-yl-ethoxy)-2-(tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 7599).

5-hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (0.53 g, 2.34 mmol) was charged in a sealed tube. Anhydrous DMF (3 mL) and Cs_2CO_3 (0.76 g, 2.34 mmol) and NaI (0.24 g, 1.56 mmol) were successively added. After 5 min, 1-(2-chloro-ethyl)-1*H*-indole **18** (0.28 g, 1.56 mmol) was added. The sealed tube was heated at 90 °C for 1 h. After cooling, DMF was removed *in vacuo*. Ethyl acetate (200 mL) was added and the solution was washed with KOH 0.1 N (2 x 10 mL), H_2O (10 mL) and finally with brine (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by chromatography on silica using as eluent $MeOH:CH_2Cl_2$ = 1:99 to 20:80. After evaporation A beige solid **EHT 7599** (0.29 mg, 50 % yield) was obtained.



MW: 369.41; Yield: 50 %; Beige solid; Mp: 97.7 °C.

R$_f$: 0.30 (CH_2Cl_2/EtOAc: 8/2).

^{1}H-NMR ($CDCl_3$, δ): 1.52-1.84 (m, 6H, CH_2-CH_2-CH_2), 3.49-3.55 (m, 1H, OCH_2), 3.75-3.83 (m, 1H, OCH_2), 4.25 (t, J = 5.6 Hz, 2H, NCH_2), 4.26 (d, J_{BA} = 14.5 Hz, 1H, OCH_2), 4.45 (dd, J_{AB} = 14.4 Hz, J_{ABx} = 0.7 Hz, 1H, OCH_2), 4.53 (t, J = 5.6 Hz, 2H, -OCH_2), 4.68 (t, J = 3.0 Hz, 1H, OCHO), 6.46 (s, 1H, -C=CH-), 6.51 (dd, J =

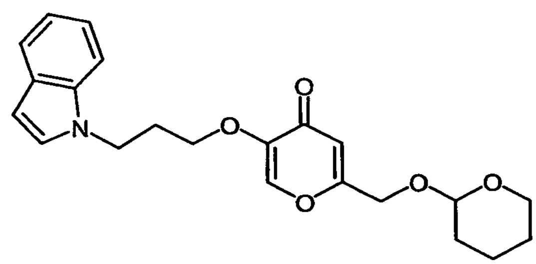
3.0 Hz, J = 0.7 Hz, 1H, Ind-H), 7.08-7.14 (m, 1H, Ind-H), 7.19-7.24 (m, 2H, Ind-H), 7.30 (s, 1H, -C=CH-), 7.37 (d, J = 8.2 Hz, 1H, Ind-H), 7.62 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 370.0 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 7599**, RT=5.78 min, peak area 99.8%.

5-(3-Indoyl-1-yl-propoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 4283).

The compound was prepared according to the above general procedure using NaH (60% dispersion in oil, 45 mg, 1.12 mmol), indole (131 mg, 1.12 mmol) and 5-(3-bromo-propoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **11** (0.30 g, 0.86 mmol). A yellow oil **EHT 4283** was obtained (70 mg, 21 % yield).



MW: 383.44, **Yield**: 21 %; Yellow oil.

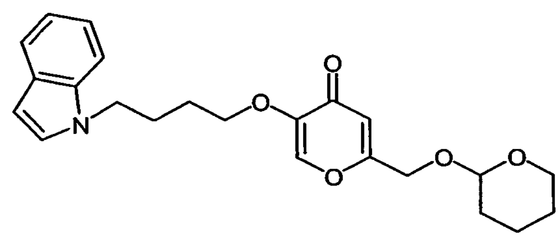
^{1}H-NMR ($CDCl_3$, δ): 1.49-1.91 (m, 6H, $3xCH_2$), 2.25-2.38 (m, 2H, CH_2), 3.50-3.59 (m, 1H, OCH_2), 3.69 (t, J = 5.8 Hz, 2H, NCH_2), 3.76-3.88 (m, 1H, OCH_2), 4.31 (d, J_{BA} = 14.4 Hz, 1H, =CCH_2O), 4.41 (t, J = 6.4 Hz, 2H, OCH_2), 4.50 (d, J_{AB} = 14.4 Hz, 1H, =CCH_2O), 4.69-4.74 (m, 1H, OC*H*O), 6.48 (d, J = 4.8 Hz, 1H, Ind-H), 6.53 (s, 1H, -C=CH-), 7.04-7.14 (m, 2H, Ind-H), 7.18 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H, Ind-H), 7.35 (d, J = 8.2 Hz, 1H, Ind-H), 7.39 (s, 1H, -C=CH-), 7.62 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 384.0 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 4283** RT = 5.94 min, peak area 92.6 %, impurity RT = 4.70 min, 7.4 %.

5-(4-Indol-1-yl-butoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5741).

The compound was prepared according to the above general procedure using NaH (60% dispersion in oil, 43 mg, 1.08 mmol), indole (126 mg, 1.08 mmol) and 5-(4-bromo-butoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **12** (0.30 g, 0.83 mmol). A yellow oil **EHT 5741** was obtained (143 mg, 43.5 % yield).



MW: 397.46, Yield: 43.5 %; Yellow oil.

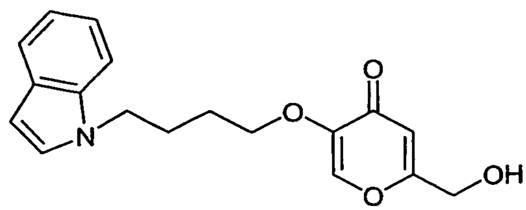
^{1}H-NMR ($CDCl_3$, δ): 1.51-1.90 (m, 8H, 4xCH_2), 1.98-2.10 (m, 2H, CH_2), 3.50-3.59 (m, 1H, OCH_2), 3.75-3.87 (m, 3H, NCH_2 and CH_2CH_2O), 4.22 (t, J = 6.8 Hz, 2H, OCH_2), 4.32 (dd, J_{BA} = 14.4 Hz, J = 0.5 Hz, CH_2O), 4.50 (dd, J_{AB} = 14.4 Hz, J = 0.5 Hz, CH_2O), 4.69-4.73 (m, 1H, OCHO), 6.47-6.51 (m, 2H, Ind-H and -C=CH-), 7.05-7.14 (m, 2H, Ind-H), 7.20 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H, Ind-H), 7.35 (d, J = 8.2 Hz, 1H, Ind-H), 7.44 (s, 1H, -C=CH-), 7.62 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 398 ([MH]$^+$, 100), 172 (20).

HPLC: Method A, detection UV 254 nm, **EHT 5741** RT = 6.16 min, peak area 95.7 %, impurities RT = 5.05 min, 1.5 %, RT = 5.25 min, 1.3 %, RT = 6.83, 1%.

2-Hydroxymethyl-5-(4-indol-1-yl-butoxy)-4*H*-pyran-4-one (EHT 3089).

EHT 5741 (50 mg, 0.125 mmol) was charged in a 3 mL vial equipped with a magnetic stirrer. 2.5 mL of MeOH and activated DOWEX (50WX8) (50 mg) were added. The reaction mixture was stirred 2 h at room temperature. The suspension was filtered and washed with methanol. After evaporation of the filtrate a yellow pale oil **EHT 3089** (24 mg, 60 % yield) was obtained.



MW: 313.35, Yield: 60 %; Yellow pale oil.

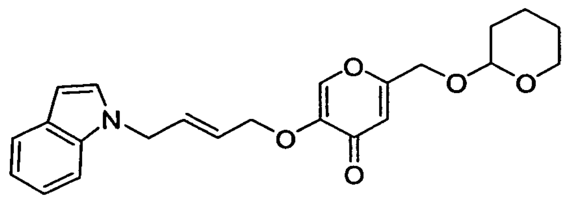
^{1}H-NMR ($CDCl_3$, δ): 1.72-1.83 (m, 2H, CH_2), 1.97-2.09 (m, 2H, CH_2), 2.98 (s broad, 1H, -OH), 3.76 (t, 2H, J = 7.2 Hz, $-NCH_2$), 4.21 (t, J = 6.8 Hz, 2H, CH_2O), 4.45 (s, 2H, CH_2OH), 4.69-4.73 (m, 1H, OCHO), 6.46-6.51 (m, 2H, Ind-H and -C=CH-), 7.04-7.13 (m, 2H, Ind-H), 7.19 (dd, J = 8.2 Hz, J = 8.2 Hz, 1H, Ind-H), 7.34 (d, J = 8.2 Hz, 1H, Ind-H), 7.41 (s, 1H, -C=CH-), 7.62 (d, J = 8.0 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 314 ($[MH]^+$, 35), 172 (100).

HPLC: Method A, detection UV 254 nm, EHT 3089 RT = 5.12 min, peak area 94.1 %, impurities RT = 3.72 min, 4.2 %, RT = 1.64 min, 1.6 %.

5-(4-Indol-1-yl-(*trans*)-but-2-enyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6895).

1*H*-Indole (37 mg, 0.32 mmol) and 5-(4-bromo-but-2-enyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **13** (0.1 g, 0.24 mmol) were charged in a 25 mL round-bottomed flask equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMSO (2 mL) and NaH 60% dispersion in oil (13 mg, 0.32 mmol) were successively. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured in 50 mL of H_2O, extracted with AcOEt (3 x 70 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, Cyclohexane:AcOEt = 8:2) to give **EHT 6895** (18 mg, 16 % yield) as an oil.



MW: 395.45, Yield: 16 %; Brown oil.

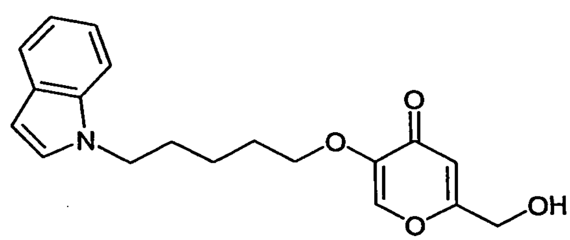
^{1}H-NMR ($CDCl_3$, δ): 0.8-1.9 (m, 6H, 3xCH_2), 3.50-3.60 (m, 1H, OCH_2), 3.75-3.90 (m, 1H, OCH_2), 4.31 (d, J = 15.0 Hz, 1H, OCH_2), 4.36 (d, J =6.0 Hz, 2H, NCH_2), 4.51 (d, J= 15.0, OCH_2, 1H), 4.72 (t, J = 3.3 Hz, 1H, OCHO), 4.77 (d, J = 4.7 Hz, 2H, OCH_2), 5.66 (dt, J_{AB} = 5.8 Hz, J_{BA}=15.5 Hz, 1H, -C=CH), 6.0 (J_{AB} = 5.3 Hz, J_{BA}=15.5 Hz, 1H, -C=CH), 6.49 (s, 1H, -C=CH), 6.52 (d, J = 3.2 Hz, 2H, Ind-H), 7.05-7.15 (m, 2H, Ind-H), 7.18 (t, J = 6.9 Hz, 1H, Ind-H), 7.50 (s, 1H, -C=CH), 7.63 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 396.1 ([MH]$^+$, 100), 170.0 (40).

HPLC: Method A, detection UV 254 nm, **EHT 6895** RT = 6.06 min, peak area 97.1 %.

2-Hydroxymethyl-5-(5-indol-1-yl-pentyloxy)-4*H*-pyran-4-one (EHT 6353).

EHT 7365 in MeOH and activated DOWEX (50WX8) were stirred 2 h at room temperature. The suspension was filtered and the precipitate was washed MeOH. After evaporation an orange solid **EHT 6353** (67 % yield) was obtained.



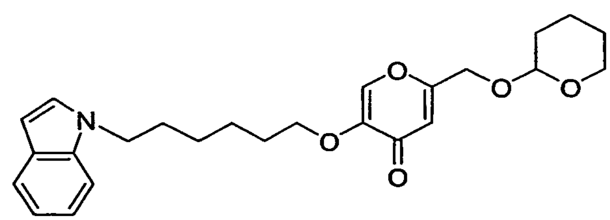
MW: 327.37; Yield: 67 %; Orange solid; Mp = 141.9 °C.

^{1}H-NMR ($CDCl_3$, δ): 1.48-1.70 (m, 3H, OH and CH_2), 1.77-1.84 (m, 2H, CH_2), 1.84-2.00 (m, 2H, CH_2), 3.45 (t, J = 6.6 Hz, 2H, -NCH_2), 3.85 (t, J = 6.3 Hz, 2H, OCH_2), 4.69 (s, 1H, CH_2OH), 5.84 (s, 1H, -C=CH-), 6.78 (d, J = 3.6 Hz, 1H, Ind-

H), 7.24-7.39 (m, 2H, Ind-H), 7.53 (d, J = 7.8 Hz, 1H, Ind-H), 7.65 (d, J = 7.8 Hz, 1H, Ind-H), 7.67 (s, 1H, -C=CH-), 8.04 (d, J = 3.6 Hz, 1H, Ind-H).

5-(5-Indol-1-yl-hexyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2358).

1*H*-Indole (299 mg, 2.55 mmol) and 5-(6-bromo-hexyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **15** (0.2 g, 0.51 mmol) were charged in a 25 mL round-bottomed flask equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMSO (2 mL) and NaH 60% dispersion in oil (23 mg, 0.56 mmol) were successively. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured in 50 mL of H_2O, extracted with AcOEt (3 x 70 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, Cyclohexane:AcOEt = 8:2) to give **EHT 2358** (33 mg, 15 % yield) as a brown oil.



MW: 425.52; Yield: 15 %; Brown oil.

R$_f$: 0.3 (EtOAc:Cyclohexane = 20:80).

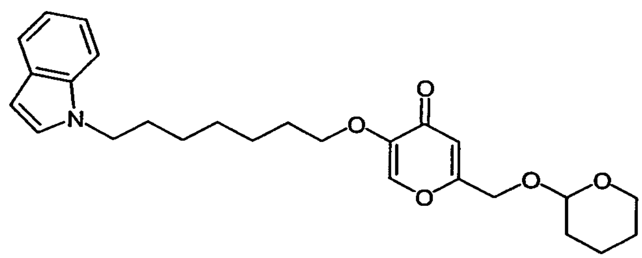
^{1}H-NMR ($CDCl_3$, δ): 1.15-1.85 (m, 14H, $7xCH_2$), 3.45-3.55 (m, 1H, OCH_2), 3.68-3.78 (m, 3H, OCH_2 and NCH_2), 4.06 (t, J_{AB} = 6.8 Hz, 2H, OCH_2), 4.26 (d, J = 14.4 Hz, 1H, OCH_2), 4.45 (d, J = 3.2 Hz, 1H, OCH_2), 4.65 (t, J = 3.2 Hz, 1H, OCHO), 6,41 (d, 1H, J = 3.1Hz, Ind-H), 6.43 (s, 1H, –C=CH), 6.98-7.06 (m, 2H, Ind-H), 7,13 (d, J = 8,0 Hz, 1H, Ind-H), 7,27 (d, J = 8.1 Hz, 1 H, Ind-H), 7.43 (s, 1H, –C=CH), 7.56 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 426.3 ([MH]$^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 2358** RT = 6.62 min, peak area > 99%.

5-(8-Indol-1-yl-heptyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8733).

The compound was prepared according to the above general procedure using NaH (60% dispersion in oil, 40 mg, 1.00 mmol), indole (117 mg, 1.00 mmol) and 5-(7-bromo-heptyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **16** (0.30 g, 0.77 mmol). A yellow brown oil **EHT 8733** was obtained (132 mg, 39 % yield).



MW: 439.54 Yield: 39 %; Yellow brown oil.

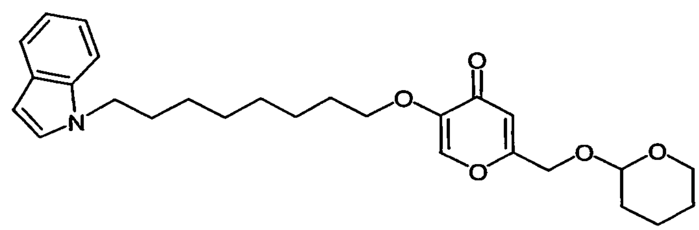
^{1}H-NMR ($CDCl_3$, δ): 1.23-1.92 (m, 16H, 8xCH_2), 3.50-3.59 (m, 1H, CH_2OCH_2), 3.77-3.87 (m, 3H, CH_2OCH_2 and NCH_2), 4.12 (t, J = 7.1 Hz, 2H, OCH_2), 4.32 (d, J_{BA} = 14.4 Hz, 1H, CH_2O), 4.53 (d, J_{AB} = 14.4 Hz, 1H, CH_2O), 4.69-4.74 (m, 1H, OCHO), 6.48 (dd, J = 3.1 Hz, 1H, Ind-H), 6.50 (s, 1H, -C=CH-), 7.05-7.13 (m, 2H, Ind-H), 7.20 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H, Ind-H), 7.34 (d, J = 8.2 Hz, 1H, Ind-H), 7.52 (s, 1H, -C=CH-), 7.62 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 440 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 8733** RT = 6.90 min, peak area 95.9 %, impurities RT = 5.26 min, 2.0 %, RT = 6.35 min, 1.1 %.

5-(8-Indol-1-yl-octyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2271).

The compound was prepared according to the above general procedure using NaH (60% dispersion in oil, 37 mg, 0.93 mmol), indole (109 mg, 0.93 mmol) and 5-(7-bromo-octyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **17** (0.30 g, 0.72 mmol). A yellow oil **EHT 2271** was obtained (127 mg, 39 % yield).



MW: 453.25; Yield: 39 %; Yellow oil.

^{1}H-NMR ($CDCl_3$, δ): 1.18-1.93 (m, 18H, 9xCH_2), 3.50-3.59 (m, 1H, CH_2OCH_2), 3.77-3.87 (m, 3H, -NCH_2 and CH_2CH_2O), 4.11 (t, J = 7.1 Hz, 2H, CH_2O), 4.42 (dd, J_{BA} = 14.3 Hz, J = 0.8 Hz, 1H, CH_2O), 4.63 (dd, J_{AB} = 14.3 Hz, J = 0.8 Hz, 1H, CH_2O), 4.70-4.74 (m, 1H, OCHO), 6.48 (dd, J = 3.1 Hz, J = 0.8 Hz, 1H, Ind-H), 6.50 (s, 1H, -C=CH-), 7.05-7.13 (m, 2H, Ind-H), 7.21 (ddd, J = 8.2 Hz, J = 1.2 Hz, 1H, Ind-H), 7.34 (d, J = 8.2 Hz, 1H, Ind-H), 7.53 (s, 1H, -C=CH-), 7.62 (d, J = 7.8 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 454 ($[MH]^+$, 100), 370 (10).

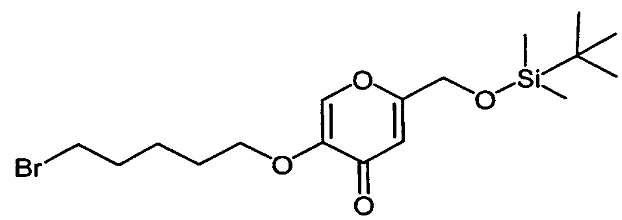
HPLC: Method A, detection UV 254 nm, **EHT 2271** RT = 7.18 min, peak area 98.9 %, impurity RT = 6.83 min, 1.0 %.

Synthesis of EHT 9238, EHT 5909, EHT 2168, EHT 1494, EHT 7365 and EHT 7168.

5-(5-Bromo-pentyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-4*H*-pyran-4-one 19.

2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-hydroxy-4*H*-pyran-4-one x (1.50 g, 5.85 mmol) was charged in a 100 mL round-bottomed flask equipped with a

magnetic stirrer and under inert atmosphere. Anhydrous DMF (25 mL) and Cs_2CO_3 (2.10 g, 6.44 mmol) were successively added. After 5 min, 1,5-dibromopentane (2.39 mL, 17.55 mmol) was added via syringe at room temperature. The reaction mixture was heated at 50°C for 3 h. After cooling and filtration DMF was removed *in vacuo*. The crude oil was purified by chromatography on silica using as eluent AcOEt:cyclohexane = 20:80 then 30:70. After evaporation, 5-(5-bromo-pentyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-4*H*-pyran-4-one **19** was obtained (1.25 g, 53% yield) as a white solid.



MW: 405.40; Yield: 53 %; White solid; Mp = 65.3 °C.

R$_f$: 0.65 (AcOEt:Cyclohexane = 50:50).

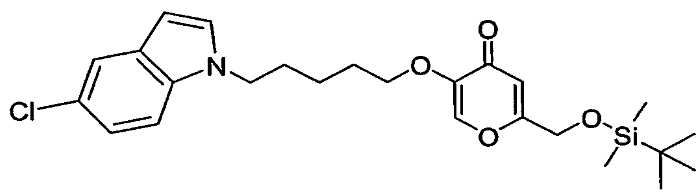
^{1}H-NMR (CD_3Cl, δ): 0.11 (s, 6H, $2xCH_3$), 0.93 (s, 9H, $3xCH_3$), 1.52-1.68 (m, 2H, CH_2), 1.79-1.97 (m, 4H, $2xCH_2$), 3.43 (t, J = 6.7 Hz, 2H, CH_2Br), 3.88 (t, J = 6.4 Hz, 2H, CH_2O), 4.46 (s, 2H, CH_2OSi), 6.50 (d, J = 0.5 Hz, 1H, –C=CH-), 7.54 (s, 1H, –C=CH).

^{13}C-NMR (CD_3Cl): 174.58, 166.84, 147.81, 139.00, 111.71, 69.38, 61.21, 33.53, 32.36, 28.21, 25.73, 24.58, 18.26, -5.48.

__2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-[5-(5-chloro-indol-1-yl)-pentyloxy]-4*H*-pyran-4-one 20.__

5-Chloroindole (0.41 g, 2.72 mmol) was charged in a 50 mL round-bottomed flask equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (15 mL) and NaH 60% dispersion in oil (109 mg, 2.72 mmol) were successively added. After 30 min 5-(5-bromo-pentyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-4*H*-pyran-4-one **19** (1.00 g, 2.47 mmol) was added at room

temperature. The reaction mixture was stirred for 2 h 30 at room temperature. The reaction mixture was pourred in 500 mL of H_2O, extracted with AcOEt (3 x 100 mL). The organic layer was washed with brine (4 x 100 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude orange oil was purified by chromatography on silica using as eluent AcOEt:cyclohexane = 2:8 to 10:0. After evaporation, 2-(tert-butyl-dimethyl-silanyloxymethyl)-5-[5-(5-chloro-indol-1-yl)-pentyloxy]-4*H*-pyran-4-one **20** was obtained (0.91 g, 77 % yield) as an orange oil.

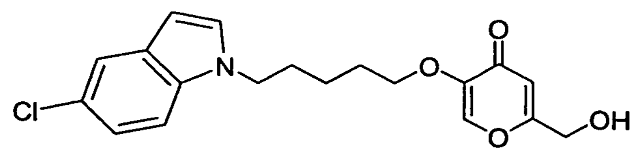


MW: 476.08; Yield: 77 %; Orange oil.

^{1}H-NMR ($CDCl_3$, δ): 0.11 (s, 6H, $2xCH_3$), 0.92 (s, 9H, $3xCH_3$), 1.35-1.50 (m, 2H, CH_2), 1.72-1.90 (m, 4H, $2xCH_2$), 3.78 (t, J = 6.4 Hz, NCH_2), 4.10 (t, J = 7.1 Hz, OCH_2), 4.45 (d, J = 0.9 Hz, 2H, CH_2OH), 6.40 (dd, J = 3.0 Hz, J = 0.6 Hz, 1H, Ind-H), 6.49 (d, J = 0.9 Hz, 1H, -C=CH), 7.09-7.17 (m, 2H, Ind-H), 7.20-7.25 (m, 1H, Ind-H), 7.43 (s, 1H, -C=CH), 7.55-7.56 (d, J = 1.7 Hz, 1H, Ind-H).

5-[5-(5-Chloro-indol-1-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 9238).

In a 100 mL round-bottomed flask 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-[5-(5-chloro-indol-1-yl)-pentyloxy]-4*H*-pyran-4-one **20** (0.88 g, 1.86 mmol) was dissolved in 15 mL of THF. A solution of *n*-tetrabutylammonium fluoride in THF (2.0 mL, 2.04 mmol) was added *via* syringe. The raction mixture was stirred 40 min at RT. The reaction mixture was evaporated *in vacuo* and the crude product was purified by chromatography on silica using as eluent AcOEt. After evaporation a yellow solid **EHT 9238** (0.55 g, 82 % yield) was obtained.



MW: 361.82; Yield: 82%; Yellow solid; Mp: 97.1 °C.

R$_f$: 0.35 (AcOEt)

^{1}H-NMR ($CDCl_3$, δ): 1.27-1.44 (m, 2H, CH_2), 1.74-1.87 (m, 4H, $2xCH_2$), 3.71-3.76 (t, J = 6.3 Hz, NCH_2), 4.06-4.11 (t, J = 7.1 Hz, OCH_2), 4.44 (s, 2H, CH_2OH), 6.39-6.40 (d, J = 3.0 Hz, 1H, Ind-H), 6.49 (s, 1H, -C=CH), 7.09-7.13 (m, 2H, Ind-H), 7.20-7.25 (m, 1H, Ind-H), 7.43 (s, 1H, -C=CH), 7.55-7.56 (d, J = 1.3 Hz, 1H, Ind-H).

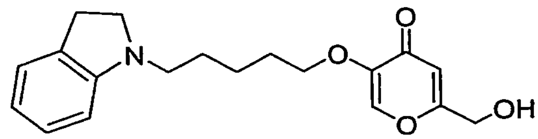
MS-ESI *m/z* (rel. int.): 361.9 ([MH]$^+$, 100), 220 (70).

HPLC: Method A, detection UV 254 nm, **EHT 9238** RT = 5.68 min, peak area 92.3 %.

Synthesis of EHT 8650, EHT 0248, EHT 3065, EHT 9546 and EHT 9853.

5-[5-(2,3-Dihydro-indol-1-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 8650).

2,3-Dihydro-1*H*-indole (0.26 g, 2.17 mmol) was charged in a 30 mL sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous EtOH (5 mL), K_2CO_3 (0.21 g, 1.55 mmol), 5-(5-bromo-pentyloxy)-2-hydroxymethyl-4*H*-pyran-4-one **1** (0.45 g, 1.55 mmol) were successively added. The reaction mixture was stirred for 6 h at reflux. After evaporation, the reaction mixture was poured in 40 mL of H_2O, extracted with AcOEt (3 x 80 mL). The organic layer was washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, CH_2Cl_2:ethyl Acetate = 8:2 to 5:5) to give after evaporation **EHT 8650** (265 mg, 52 % yield) as a light brown solid.



MW: 329.39; Yield: 52 %; Brown solid; Mp: 106.8 °C.

R_f: 0.32 (CH_2Cl_2/MeOH: 95/5).

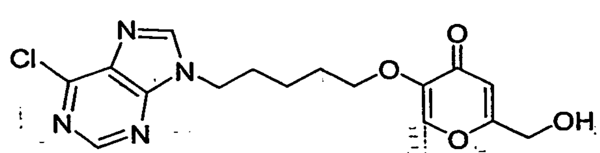
^{1}H-NMR ($CDCl_3$, δ): 1.48-1.70 (m, 4H, CH_2), 1.82-1.91 (m, 2H, CH_2), 2.94 (t, J = 8.2 Hz, 2H, Ar-CH_2), 3.05 (t, J = 7.0 Hz, 2H, NCH_2), 3.32 (t, J = 8.2 Hz, 2H, NCH_2), 3.78 (s, 1H, OH), 3.84 (t, J = 6.5 Hz, 2H, O-CH_2), 4.46 (s, 2H, CH_2OH), 6.45 (d, J = 7.6 Hz, 2H, Ar-H), 6.51 (s, 1H, C=CH), 6.60-6.65 (m, 1H, Ar-H), 7.02-7.07 (m, 1H, Ar-H), 7.54 (s, 1H, C=CH).

MS-ESI *m/z* (rel. int.): 330.0 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, EHT **8650**, RT=3.70 min, peak area 100.0%.

<u>5-[5-(6-Chloro-purin-9-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 0248).</u>

6-Chloro-9*H*-purine (0.27 g, 1.75 mmol) was charged in a 30 mL sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (5 mL), triethylamine (0.40 g, 4.00 mmol), 5-(5-bromo-pentyloxy)-2-hydroxymethyl-4*H*-pyran-4-one **1** (0.51 g, 1.75 mmol) were successively added. The reaction mixture was stirred for 15 h at 70 °C. After evaporation, the reaction mixture was poured in 50 mL of H_2O, extracted with AcOEt (3 x 100 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, CH_2Cl_2:MeOH = 98:2 to 95:5) to give after evaporation **EHT 0248** (215 mg, 34 % yield) as a white powder.



MW: 364.78; Yield: 34 %; White solid; Mp: 129.5 °C.

***R**f*: 0.22 (EtOAc).

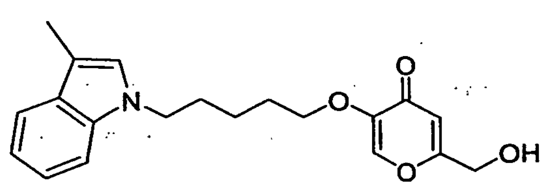
^{1}H-NMR ($CDCl_3$, δ): 1.47-1.57 (m, 2H, CH_2), 1.80-1.89 (m, 2H, CH_2), 1.95-2.05 (m, 2H, CH_2), 3.82 (t, J = 6.0 Hz, 2H, NCH_2), 4.34 (t, J = 7.1 Hz, 2H, OCH_2), 4.40 (t, J = 6.0 Hz, 1H, OH exchangeable with D_2O), 4.49 (d, J = 5.9 Hz, 2H, -CH_2OH), 6.51 (s, 1H, C=CH), 7.54 (s, 1H, C=CH), 8.26 (s, 1H, H-Pur), 8.72 (s,1H, H-Pur).

MS-ESI *m/z* (rel. int.): 365.0/367.0 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 0248**, RT=3.80 min, peak area 98.0%.

2-Hydroxymethyl-5-[5-(3-methyl-indol-1-yl)-pentyloxy]-4*H*-pyran-4-one (EHT 3065).

3-Methyl-1*H*-indole (0.27 g, 2.06 mmol) was charged in a 30 mL sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (3 mL) and NaH 60% dispersion in oil (82 mg, 2.06 mmol) were successively added. After 30 min a solution of 5-(5-bromo-pentyloxy)-2-hydroxymethyl-4*H*-pyran-4-one **1** (0.30 g, 1.03 mmol) in anhydrous DMF (3mL) was added. The reaction mixture was stirred for 2 h at 20 °C and 0.5 h at 60°C. The reaction mixture was poured in 200 mL of H_2O, acidified with HCl 1N (5 mL), extracted with CH_2Cl_2 (3 x 75 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, AcOEt) to give after evaporation **EHT 3065** (30 mg, 8 % yield) as a colorless oil.



MW: 341.40; Yield: 8 %; Colorless oil.

R_f: 0.32 (EtOAc).

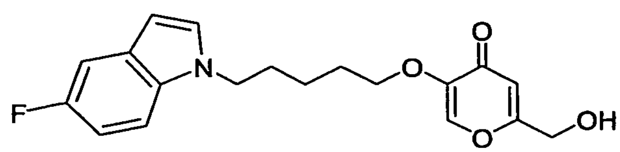
^{1}H-NMR ($CDCl_3$, δ): 1.31-1.46 (m, 2H, CH_2), 1.72-1.84 (m, 4H, CH_2), 2.28 (s, 3H, CH_3), 3.40 (s, 1H, OH), 3.73 (t, J = 6.4 Hz, 2H, NCH_2), 4.04 (t, J = 6.9 Hz, 2H, O-CH_2), 4.42 (s, 2H, O-CH_2), 6.47 (s, 1H, C=CH), 6.82 (s, 1H, Ind-H), 7.05 (t, J = 6.9 Hz, 1H, Ind-H), 7.15 (t, J = 7.0 Hz, 1H, Ind-H), 7.22-7.26 (m, 1H, Ind-H), 7.42 (s, 1H, C=CH), 7.52 (d, J = 7.9 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 342.0 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 3065** RT=5.60 min, purity 95.0%.

<u>5-[5-(5-fluoro-indol-1-yl)-pentyloxy]-2-Hydroxymethyl-4*H*-pyran-4-one (EHT 9546).</u>

EHT 0533 (0.45 g, 1.00 mmol) was charged in a 50 mL round-bottomed flask equipped with a magnetic stirrer. 25 mL of MeOH and activated DOWEX (50WX8) (1.40 mg) were added. The reaction mixture was stirred 10 min at room temperature. The suspension was filtered and after evaporation a viscous yellow pale oil (310 mg, 90 % crude yield) was recristallized with AcOEt to give after filtration and drying **EHT 9546** (170 mg, 50 % yield)) as a white solid.



MW: 345.36; Yield: 50 %; White solid; Mp: 119.3 °C.

R_f: 0.28 (EtOAc).

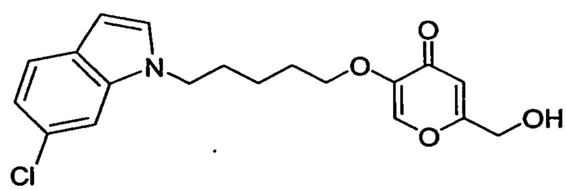
^{1}H-NMR ($CDCl_3$, δ): 1.42-1.49 (m, 2H, CH_2), 1.75-1.92 (m, 4H, CH_2), 3.76 (t, J = 6.3 Hz, 2H, NCH_2), 4.11 (t, J = 6.8 Hz, 2H, O-CH_2), 4.46 (s, 2H, O-CH_2), 6.42 (d, J = 2.8 Hz, 1H, Ind-H), 6.51 (s, 1H, C=CH), 6.93 (ddd, J = 9.0 Hz, J = 2.1 Hz, 1H, Ind-H), 7.13 (d, J = 2.8 Hz, 1H, Ind-H), 7.21-7.26 (m, 2H, Ind-H), 7.46 (s, 1H, C=CH).

MS-ESI *m/z* (rel. int.): 346.0. ([MH]$^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 9546** RT=5.50 min, peak area 95.0%.

5-[5-(6-chloro-indol-1-yl)-pentyloxy]-2-Hydroxymethyl-4*H*-pyran-4-one (EHT 9853).

EHT 8617 (0.60 g, 1.34 mmol) was charged in a 50 mL round-bottomed flask equipped with a magnetic stirrer. 20 mL of MeOH and activated DOWEX (50WX8) (2.40 mg) were added. The reaction mixture was stirred 12 min at room temperature. The suspension was filtered and after evaporation a viscous yellow pale oil (400 mg, 82 % crude yield) was purified by column chromatography (SiO_2, AcOEt) to give after evaporation and drying **EHT 9853** (130 mg, 35 % yield)) as a brown oil.



MW: 361.82; Yield: 35 %; Brown oil.

***R*$_f$**: 0.28 (EtOAc).

^{1}H-NMR ($CDCl_3$, δ): 1.26-1.45 (m, 2H, CH_2), 1.70-1.84 (m, 4H, CH_2), 3.69 (t, *J* = 6.3 Hz, 2H, NCH_2), 4.03 (t, *J* = 7.0 Hz, 2H, O-CH_2), 4.43 (s, 2H, O-C*H*$_2$OH), 4.74 (s, 1H, O-CH_2O*H*), 6.42 (dd, *J* = 3.1 Hz, *J* = 0.6 Hz, 1H, Ind-H), 6.50 (s, 1H, C=CH), 7.02 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H, Ind-H), 7.05 (d, *J* = 3.1 Hz, 1H, Ind-H), 7.30 (s, 1H, Ind-H), 7.44 (s, 1H, C=CH), 7.48 (d, *J* = 8.4 Hz, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 362.0/364.0 ([MH]$^+$, 100).

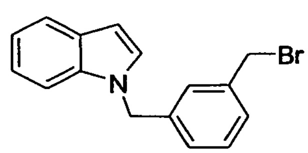
HPLC: Method A, detection UV 254 nm, **EHT 9853** RT=5.80 min, peak area 99.9%.

Synthesis of EHT 8589, EHT 3986 and EHT 4336.

Synthesis of intermediates 21, 22 and 23.

1-(3-Bromomethyl-benzyl)-1*H*-indole 21.

1*H*-Indole (1.00 g, 8.45 mmol) and DMF (18 mL) were charged in a 25 mL round-bottomed flask equipped with a magnetic stirrer and under inert atmosphere. NaH 60% dispersion in oil (370 mg, 9.30 mmol) was added at 0°C. The reaction mixture was added slowly to a solution of 1,3-bis-bromomethyl-benzene (2.3 mg, 8.45 mmol) in DMF (6 mL) at 0°C and stirred for 0.5 h at room temperature. The reaction mixture was poured in 50 mL of ice, extracted with AcOEt (3 x 70 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, cyclohexane:AcOEt = 99:1 to 96:4) to give 1-(3-bromomethyl-benzyl)-1*H*-indole **21** (380 mg, 15 % yield) as an oil.



MW: 300.19; Yield: 15 %; colorless oil.

R*f*: 0.37 (Cyclohexane:Ethyl Acetate = 9:1).

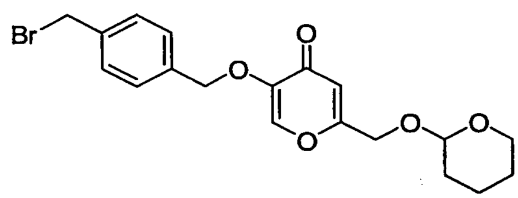
^{1}H-NMR ($CDCl_3$, δ): 4.40 (s, 2H, $BrCH_2$), 5.30 (s, 2H, NCH_2), 6.54 (dd, *J* = 3.1 Hz, *J* = 0.7 Hz, 1H, Ind-H), 6.98 (d, *J* = 6.7 Hz, 1H, Ind-H), 7.07-7.26 (m, 7H, Ar-H, Ind-H), 7.62-7.65 (m, 1H, Ind-H).

MS-ESI *m/z* (rel. int.): 300.0-302.0 ($[MH]^+$, 100).

HPLC: Method A, Detection UV 254 nm, RT= 6.93 min.

5-(4-Bromomethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 22.

5-Hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol) was charged in a 30 ml sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (15 ml), Cs_2CO_3 (1.52 g, 4.64 mmol) and 1,4-bis-bromomethyl-benzene (2.33 g, 8.84 mmol) were successively added. The reaction mixture was stirred 1 h at 90°C. After evaporation of DMF, the reaction mixture was poured in 50 mL of H_2O, extracted with AcOEt (3 x 100 mL). The organic layer was washed with KOH 0.1N (10 mL), brine (2 x 10 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, CH_2Cl_2:AcOEt 9:1 to 8:2) to give after evaporation 5-(4-bromomethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **22** as a yellow solid (400 mg, 22 % yield).



MW: 409.27; Yield: 22 %; Yellow solid; Mp = 83.5 °C.

R$_f$: 0.35 (Cyclohexane:Ethyl Acetate = 9:1).

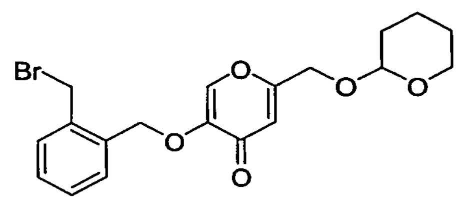
^{1}H-NMR ($CDCl_3$, δ): 1.53-1.84 (m, 6H, CH_2), 3.52-3.57 (m, 1H, OCH_2), 3.77-3.84 (m, 1H, OCH_2), 4.30 (d, J_{BA} = 14.5 Hz, 1H, OCH_2), 4.48 (s, 2H, OCH_2), 4.50 (d, J_{AB} = 14.5 Hz, 1H, OCH_2), 4.70 (t, J = 3.1 Hz, 1H, OCHO), 5.07 (s, 2H, $BrCH_2$), 6.51 (s, 1H, -C=CH-), 7.36-7.42 (m, 4H, Ar-H), 7.53 (s, 1H, -C=CH-).

MS-ESI *m/z* (rel. int.): 408.9-410.9 ($[MH]^+$, 100).

HPLC: Method A, Detection UV 254 nm, RT= 5.85 min.

5-(2-Bromomethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one 23.

5-Hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (1.00 g, 4.42 mmol) was charged in a 30 mL sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (25 mL), Cs_2CO_3 (1.58 g, 4.86 mmol) and 1,2-bis-bromomethyl-benzene (2.33 g, 8.84 mmol) were successively added. The reaction mixture was stirred 2 h at 60°C. After evaporation of DMF, the crude compound was purified by column chromatography (SiO_2, CH_2Cl_2:AcOEt = 8:2) to give after evaporation 5-(2-bromomethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **23** as an oil (188 mg, 11 % yield).



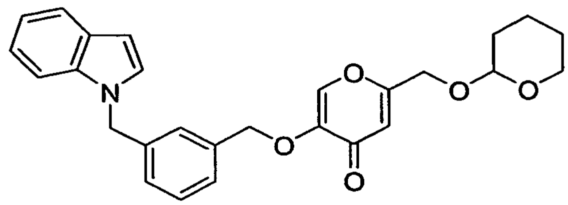
MW: 409.27, Yield: 11 %; Oil.

^{1}H-NMR ($CDCl_3$, δ): 1.43-1.95 (m, 6H, $3xCH_2$), 3.46-3.59 (m, 1H, OCH_2), 3.77-3.88 (m, 1H, OCH_2), 4.31 (d, *J* = 14.4 Hz, 1H, OCH_2), 4.50 (d, *J* = 14.4 Hz, 1H, OCH_2), 4.66 (s, 2H, CH_2Br), 4.72 (m, 1H, OCHO), 5.20 (s, 2H, CH_2O), 6.53 (s, 1H, -C=CH-), 7.28-7.45 (m, 4H, Ar-H), 7.67 (s, 1H, -C=CH-).

5-[3-Indol-1-yl-methyl-benzyloxy)-2-tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 8589).

5-Hydroxy-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (0.30 g, 1.33 mmol) was charged in a 50 mL round-bottomed flask equipped with a magnetic stirrer and under inert atmosphere. Anhydrous THF (16 mL) and NaH 60% dispersion in oil (56 mg, 1.39 mmol) were successively added. After 30 min 1-(3-bromomethyl-benzyl)-1*H*-indole **21** (0.38 g, 1.27 mmol) was added at room temperature. The reaction mixture was stirred for 10 h at reflux. The reaction mixture was poured in 100 mL of H_2O, extracted with AcOEt (3 x 60 mL). The organic layer was washed with KOH 0.1N (10 mL), brine (2 x 10 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by

column chromatography (SiO_2, CH_2Cl_2:Ethyl Acetate = 9:1 to 8:2) to give after evaporation **EHT 8589** (210 mg, 37 % yield) as a pasty product.



MW: 445.51; Yield: 37 %; Colorless oil.

***R**f*: 0.50 (CH_2Cl_2/EtOAc: 8/2).

^{1}H-NMR ($CDCl_3$, δ): 1.57-1.85 (m, 6H, CH_2-CH_2-CH_2), 3.51-3.57 (m, 1H, O-CH_2), 3.78-3.86 (m, 1H, O-CH_2), 4.29 (d, J_{BA} = 14.4 Hz, 1H, O-CH_2), 4.49 (d, J_{AB} = 14.4 Hz, 1H, O-CH_2), 4.71 (t, J = 3.0 Hz, 1H, CH), 5.00 (s, 2H, N-CH_2), 5.33 (s, 2H, O-CH_2), 6.50 (s, 1H, C=CH), 6.56 (d, J = 3.1 Hz, 1H, Ar-H), 7.03-7.30 (m, 8H, Ar-H), 7.40 (s, 1H, C=CH), 7.65 (d, J = 7.7 Hz, 1H, Ar-H).

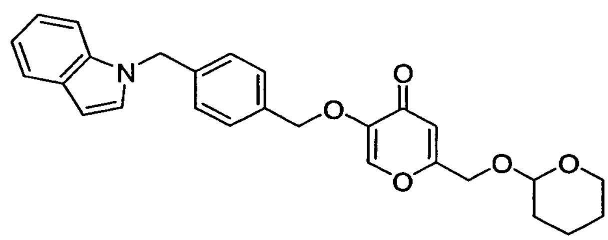
MS-ESI *m/z* (rel. int.): 446.1 ($[MH]^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 8589**, RT=6.47 min, peak area 99.5%.

<u>5-[4-Indol-1-yl-methyl-benzyloxy)-2-tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 3986).</u>

1*H*-Indole (137 mg, 1.17 mmol) was charged in a 30 mL sealed tube equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMF (5 mL) and NaH 60% dispersion in oil (50 mg, 1.25 mmol) were successively added at 4 °C. After 30 min a solution of 5-(4-bromomethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **22** (0.40 g, 0.98 mmol) in DMF (2 mL) was added at 4°C. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured in 50 mL of H_2O, extracted with AcOEt (3 x 70 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column

chromatography (SiO_2, CH_2Cl_2:AcOEt = 9:1 to 8:2) to give **EHT 3986** (220 mg, 50 % yield) as a beige solid.



MW: 445.51; Yield: 50 %; Beige solid; Mp: 93.3 °C.

***R**f*: 0.47 (CH_2Cl_2/EtOAc: 8/2).

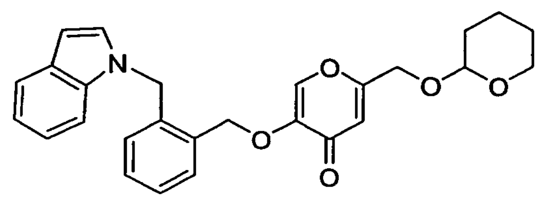
^{1}H-NMR ($CDCl_3$, δ): 1.58-1.84 (m, 6H, CH_2-CH_2-CH_2), 3.51-3.56 (m, 1H, OCH_2), 3.77-3.83 (m, 1H, OCH_2), 4.29 (d, J_{BA} = 14.4 Hz, 1H, OCH_2), 4.48 (d, J_{AB} = 14.4 Hz, 1H, OCH_2), 4.70 (t, J = 3.0 Hz, 1H, CH), 5.02 (s, 2H, NCH_2), 5.33 (s, 2H, OCH_2), 6.50 (s, 1H, -C=CH-), 6.55 (d, J = 3.1 Hz, 1H, Ar-H), 7.09-7.33 (m, 8H, Ar-H), 7.49 (s, 1H, -C=CH-), 7.65 (d, J = 7.8 Hz, 1H, Ar-H).

MS-ESI *m/z* (rel. int.): 446.1 ([MH]$^+$, 100).

HPLC: Method A, detection UV 254 nm, **EHT 3986**, RT=6.45 min, peak area 99.5%.

5-(2-Indol-1-ylmethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 4336).

1*H*-Indole (37 mg, 0.32 mmol) and 5-(2-bromomethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one **23** (0.10 g, 0.28 mmol) were charged in a 25 mL round-bottomed flask equipped with a magnetic stirrer and under inert atmosphere. Anhydrous DMSO (2 mL) and NaH 60% dispersion in oil (13 mg, 0.32 mmol) were successively. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured in 50 mL of H_2O, extracted with AcOEt (3 x 70 mL). The organic layer was washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by column chromatography (SiO_2, Cyclohexane:AcOEt = 8:2) to give **EHT 4336** (23 mg, 21 % yield) as an oil.



MW: 445.51, Yield: 21 %; Brown oil.

^{1}H-NMR ($CDCl_3$, δ): 1.45-1.80 (m, 6H, $3xCH_2$), 3.42-3.55 (m, 1H, OCH_2), 3.70-3.82 (m, 1H, OCH_2), 4.24 (d, *J* = 14.5 Hz, 1H, OCH_2), 4.43 (d, *J* = 14.5 Hz, 1H, OCH_2), 4.65 (t, *J* = 3.0 Hz, 1H, OCHO), 4.86 (s, 2H, CH_2N), 5.43 (s, 2H, CH_2O), 6.45 (s, 1H, -C=CH-), 6.47 (d, *J* = 3.1 Hz, *J* = 0.6 Hz, 1H, Ar-H), 6.84 (dd, *J* = 2.0 Hz, *J* = 7.7 Hz, 1H, Ar-H), 7.03 (ddd, *J* = 1.7 Hz, *J* = 7.2 Hz, *J* = 15.33 Hz, 2H, Ar-H), 7.16-7.23 (m, 4H, Ar-H), 7.30 (s, 1H, -C=CH-), 7.58 (dd, *J* = 2.0 Hz, *J* = 6.9 Hz, 1H, Ar-H)

MS-ESI *m/z* (rel. int.): 446.1 ($[MH]^+$, 100), 220.1 (45).

HPLC: Method A, detection UV 254 nm, **EHT 4336** RT = 6.89 min, peak area >99 %.

Example 31 : Pharmacology

This example discloses a series of assays used to illustrate the biological activity of the compounds.

Methods

A series of tests was designed to screen the various compounds and evaluate their direct effect on small GTPases activities as well as their anti-proliferative and anti-tumor potential. Compound L651582 CAI (carboxyamidotriazole) was included as a positive control for G-protein mediated signalling inhibition (Kohn et al., J. Natl. Cancer Inst., 1990).

a) Cell Culture and Cytotoxicity Assay

Four human tumoral cell lines, namely HCT116 colon adenocarcinoma, H460 lung carcinoma, MCF-7 and MDA-MB-231 breast carcinoma cell lines, and three

immortalized but non tumorigenic cell lines, namely NIH3T3 mouse fibroblasts and human breast-derived MCF10-A and MRC-5 were purchased at ATCC and cultured according to their recommendations. In order to determine the cytotoxicity associated with one compound, a microculture tetrazolium assay (MTT), as described by Carmichael *et al* (Cancer Res, 1996) with modifications, was used. Briefly, 5.10^3 or 2.10^4 cells were seeded per well in 24-well plates 24 hours before drug addition. Cells were treated with 0, 1, 10, 17.5, 25 and 50µM of compound solubilized in DMSO, adjusting the total volume of DMSO (Dimethylsulfoxide) to 1%. Forty-eight hours or 6 days after treatment, the medium was replaced by PBS containing 0.5mg/ml MTT (Sigma) and cells were incubated for 3 more hours at 37°C before solubilization of formazan crystals in 100% DMSO. Absorbance was measured using a spectrophotometer at a wavelength of 550nm . Cell surviving fraction and 50% inhibitory concentration were calculated. All assays were performed in triplicate.

b) Anchorage-independent growth assay

In order to evaluate the effect of the compounds on the capacity of tumor cells to grow without anchorage, HCT116 cells were seeded either in agar or in Matrigel (BD, France). For 3D growth experiment in soft agar in 24-well plates, 5.10^3 HCT 116 cells were resuspended in 250µl of complete medium containing 0.3% soft-agar (Difco) and different concentrations of compound (0.1, 1, 10, 17.5, 25 and 50 µM). Cells were then poured on a solidified layer of medium containing 0.5% of soft-agar plus the compound at the same concentration than in the upper layer. Cells were incubated at 37°C for 1 week before they were analysed using a phase contrast microscope (Nikon). For 3D growth experiment in Matrigel, 10^4 HCT116 cells were resuspended in 300 µl of complete medium containing 5mg/ml Matrigel (BD, France) and different concentrations of compound (0.1, 1, 10, 17.5, 25 and 50 µM), and poured in 24-well plates. After solidification at 37°C for 15 min., complete medium containing the compound was added to each well. Cells were incubated for 1 week before they were collected using Matrisperse (BD, France) according to the manufacturer's instructions. After recovery, alive cells were counted with trypan blue exclusion.

c) Ras/ Rac-dependant signaling pathway analysis

The impact of the compounds on Ras and Rac signaling pathways was analysed with two reporter systems described by Imler (Nature 1988) and Lin (Science, 1995) respectively on one hand, and by a colony formation assay in the presence of constitutively activated Ras (RasV12) and Rac (RacV12) on the other hand. For this latter experiment, fifty percent confluent NIH3T3 cells in a 10 cm diameter petri dish were transfected with 0.5µg pSV2-RasV12 or 0.5µg pEXV RacV12 plasmids plus 100ng of pSV2-neomycin plasmid using Lipofectamine-Plus reagent (Invitrogen) according to the manufacturer's instructions. Forty-eight hours later, cells were trypsinised, splitted to 1/3, and incubated in the presence of complete medium supplemented with 400µg/ml geneticin (Invitrogen) and different doses of compound (1, 10, 17.5, 25 and 50 µM) until emerging resistant clones appear (2-3 weeks). The medium was renewed every 3 days. Colonies with a minimum of 50 cells were counted after staining with Fuschin 2%.

d) Migration and Matrigel Invasion Assay

Chemoinvasion assay was performed in Boyden chamber as described by Albini *et al* (Cancer Res, 1987) with some modifications. Polycarbonate membranes with 8µm pores were coated with matrigel (125µg/cm^2) at room temperature for 48h. Two hours before experiments, the matrix was dehydrated with serum-free medium containing 0.1% BSA.

One day after seeding, 10^6 MDA-MB-231 cells were treated overnight with different concentrations of compounds (1, 10, 17.5, 25 and 50 µM). Cells were collected with Versene (Invitrogen), counted with trypan blue exclusion, rinsed twice in serum-free medium containing 0.1% BSA and resuspended in serum-free medium containing 0.1% BSA plus the appropriate concentration of compound. 10^5 treated cells were placed in the upper chamber. Medium containing 10% of FBS plus the appropriate concentration of compound was placed in the lower chamber as a chemoattractant. The Boyden chamber was incubated 6 hours at 37°C before the cells were fixed and stained with Diff-Quick (Dade-Berhing). Cells

on the upper part of the filters were removed using a cotton swab. Cells on the underside of the filters were visualised and counted under light microscope.
The migration assay was performed the same way, using non-coated filters.

e) Gelatin Zymography

The activity of the metalloproteases MMP-2 and MMP-9 was assayed using gelatinolytic zymography according to Lambert (Surgery 1997). Briefly, MDA-MB-231 cells were incubated overnight in serum-free medium supplemented with ITS liquid supplement (Sigma) with different concentrations of compound (1, 10, 17.5, 25 and 50 μM). Supernatant was collected and concentrated with Ultrafree 30kDA (Millipore). Equal amount of proteins, as determined by Bradford measurement, were loaded onto a 10% w/v polyacrylamide gel containing 1% gelatin and 0.1% SDS (Novex). After electrophoresis, gels were washed in Novex Zymogram Renaturing buffer for 30 min at room temperature and incubated overnight at 37°C in Novex Zymogram developing buffer. Gels were stained in Coomassie Brilliant Blue G-250, and the gelatinolytic activity was visualized as a clear band against the blue background of the stained gelatin.

f) Cytoskeleton analysis

Since major rearrangements of cytoskeleton are observed in tumor cells and since the small GTPases are known to regulate these events, analysis of actin cytoskeleton was performed. Subconfluent cells seeded onto coverslips were treated with different concentration of compound (1, 10, 17.5, 25 and 50 μM) or vehicle for 24h, before being fixed in 4% formaldehyde for 15 min., permeabilized in 0.2% Triton X100 for 5 minutes and incubated in PowerBlock (Biogenex) for 10 min. Actin filaments were stained with 0.5μg/ml fluorescein isothiocyanate (FITC)-labelled phalloidin for 1 hour. Analysis was performed using an inverted fluorescent microscope.

Results

The compounds were tested through the different in vitro tests described above. Results are presented in Table 1.

Table I. Screening Results

	Toxicity 6d (IC 50, µM)							Anchorage-independent Growth (IC50)	Invasion
	H460	HCT116	MDA231	MCF7	NIH3T3	MRC-5	MCF10-A		
EH6600	>50	>50	>25	30	ND	ND	ND	-	ND
EH15700	>50	>50	20	>50	ND	ND	ND	-	ND
EH17600	>50	>50	>25	17,5	ND	ND	ND	ND	ND
EH20700	>50	>50	>50	>50	ND	ND	ND	ND	ND
EH27900	>50	>50	>25	40	ND	ND	ND	ND	ND
EH26900	>50	>50	>50	>50	ND	ND	ND	ND	ND
EH15301	>50	>50	>50	>50	>50	ND	ND	ND	ND
EH17401	>50	>50	>50	>50	>50	ND	ND	ND	ND
EH18401	>50	>50	>50	>50	>50	ND	ND	ND	ND
EH22501	>50	>50	50	>50	>50	ND	ND	ND	ND
EH10501	>50	>50	>50	>50	>50	ND	ND	ND	ND
EH26101	35	>50	40-45	>50	1-5	ND	ND	50µM	ND
EH30101	35	50	30-35	45	0,1-0,5	ND	ND	7,5µM	ND
EH16201	20	50	>50	25	25	ND	ND	12,5µM	ND
EH17700	15	30	15-20	20	ND	>50	ND	-	ND
EH5500	15	50	>50	35	ND	ND	ND	-	ND
EH15500	35	50	15	>50	ND	ND	ND	-	ND
EH10600	25	>50	10	40	ND	ND	ND	-	ND
EH22900	15	10	30	50	30	25	>50	<<1µM	Decrease
EH18900	40	35	>50	30	0,5	17,5	50	1-5µM	Increase
EH31101	25	30	25	25	>50	ND	35	<1µM	Increase
EH9301	25	20	25	20	50	35	>50	-	No effect
EH16701	7	8,5	47,5	15	>50	>50	>50	-	No effect
EH17701	5-10	5-10	35	15	ND	17,5	>50		
EH18601	25	50	>50	15	>50	ND	ND	-	No effect
EH30701	15	8	15	20	ND	ND	ND	-	Decrease
EH28900	10	25	5	20	0,5	ND	50	-	ND
EH7701	6	7,5	22,5	17,5	40	20	>50	-	No effect

	Small GTPases		Colony formation	Cell architecture modification					Migration
	activities			phase contrast	actin staining (R: ruffles ; FC : focal complexes)				
	Ras	Rac			NIH3T3	MDA231	H460	HCT116	ND
EH5500	-	-	-	+	cell destructuration	ND	ND	ND	ND
EH15500	-	ND	-	+	cell destructuration	ND	ND	ND	ND
EH17700	-	-	-	-	ND	ND	ND	ND	no effect
EH10600	-	-	-	+	cell destructuration	ND	ND	ND	ND
EH22900	-	-	+	+	R - , FC +	cell spreading	ND	ND	inhibition
EH18900	-	ND	+	+	R - , FC +	-	cell spreading	cell spreading	no effect
EH31101	-	-	-	+	R - , FC +	-	-	-	no effect
EH9301	ND	ND	-	-	ND	ND	ND	ND	no effect
EH16701	ND	ND	ND	-	ND	cell spreading	ND	ND	ND
EH17701	ND	ND	ND	-	ND	cell spreading	ND	ND	ND
EH18601	ND	ND	ND	-	ND	ND	ND	ND	ND
EH30701	ND	ND	ND	-	ND	cell spreading	ND	ND	ND
EH28900	-	ND	ND	-	ND	ND	ND	ND	ND
EH7701	ND	ND	ND	-	ND	cell spreading	ND	ND	ND

ND : Not Determined; - : no effect of the compound was observed; + : an effect of the compound was observed. Toxicity test: the sign > was used when the IC50 was not reached at the highest concentration of compound tested. Anchorage-independent growth test: a sign – was used when no difference was observed between the IC50 in 3-dimensional growth conditions and regular growth conditions (HCT116 cells in anchorage independent growth assay versus HCT116 in toxicity assay). Cell architecture : a decrease in cellular ruffles density was noted R-, an increase in focal complexes density was noted FC+. General observations are also indicated.

The compounds can be schematically divided into two groups, one with an alcohol, or a benzyloxymethyl group in position R_1 and one with an acidic or a benzylcarbamoyl group at the same position. Cytotoxicity tests showed that the first group of compounds were the most toxic on tumoral cell lines. Nine compounds were toxic on at least three of the four tumoral cell lines with IC50 after 6 days of treatment inferior to 30 μM. Compounds EH16701, EH7701, EH17701, EH30701, EH22900 and EH28900 were the most toxic with an IC 50 inferior or equal to 15μM on HCT116 after 6 days of treatment. The two compounds EH22900 and EH18900 inhibited Ras-dependent neoR clones formation (the effect of EH16701, EH7701, EH17701 and EH30701 have not been tested yet in this assay). Results are shown for compound EH22900 on Figure 1.

Compound EH22900 also showed the strongest effect on anchorage-independent growth (Figure 2). Compound EH31101 also showed a significant, although less severe, effect on anchorage-independent growth .

Whereas compounds EH5500, EH15500 and EH10600 affected the general morphology of NIH3T3 cells, as detected by β-actin staining, a specific inhibition of membrane ruffles and an increase in the number of stress fibers was observed in the case of compounds EH22900, EH18900 and EH31101, at a concentration of 10μM, 10μM and 50μM respectively. Results are shown for

compound EH22900 in Figure 3. Compound EH22900 also increased MDA-MB-231 spreading.

Concerning compound EH31101, a dose-dependant increase in spreading and a disruption of cell-to-cell junctions was observed in the presence of 25µM and 10µM of compound EH31101, on H460 and HCT116 tumor cells, respectively.

An *in vitro* evaluation of the effect of compounds EH22900, EH18900, EH17701, EH16701, EH30701, EH18601, EH7701, EH9301 and EH31101 on invasive properties of MDA-MB-231 cells showed a significant inhibition with compounds EH22900, EH17701 and EH30701 at a concentration of 17.5µM. An increase in invasive properties was noted for compounds EH18900 and EH31101 at 50µM and 10µM, respectively. No significant effect on invasion was observed with either other compound. Results are presented for compound EH22900 on Figure 4.

Inhibition of serum-induced migration was observed at 25µM for compound EH22900 and at 10µM for compound EH31101. Results are presented for compound EH22900 on Figure 5.

Finally, the ability of tumor cells to secrete the metalloproteases MMP-2 and MMP-9 in the presence of compound EH22900 or EH31101 was quantified by a zymogram gel. Compounds EH22900 and EH31100 inhibited MMP-2 and MMP-9 in a dose-dependant manner at concentrations of 5µM and 0.1µM, respectively.

These results thus illustrate the ability of the compounds of this invention (and the particular efficacy of compounds EH22900, EH30701 and EH17701) to inhibit growth of tumor cells, to affect actin architecture and specific characteristics of tumor cells such as anchorage-independent growth and invasion.

Example 32 : Pharmacology

1. Material and Methods

Another series of *in vitro* tests was designed to screen the various compounds and evaluate their anti-proliferative and anti-tumor potential.

Reference L651582 (Merck Institute for Therapeutic Research, Rahway, NJ) is a carboxyamide-amino-imidazole compound originally developed as a coccidiostat (U.S. patent No. 4,590,201). L651582 has been shown later by the NCI to be a synthetic inhibitor of both nonvoltage- and voltage-gated calcium pathways. It demonstrated inhibition of tumor cell motility, adhesion, metastatic potential, and growth *in vitro* in a number of human tumor cell lines at concentrations from 1 to 10 μM. *In vivo* activity was also shown, and the compound is currently in Phase III clinical trial for non small cell lung cancer.

Cell culture and cell viability assay

In order to determine one compound effect on cell viability, microculture tetrazolium assay (MTT) was performed as described by Carmichael *et al.* (1996) with modifications. Four human tumoral cell lines, namely HCT116 colon adenocarcinoma, H460 lung carcinoma, MCF-7 and MDA-MB-231 breast carcinoma cell lines, and 3 immortalized but non tumorigenic cell lines, namely NIH3T3 mouse fibroblasts and human breast-derived MCF10-A and human lung-derived MRC-5 were purchased at ATCC and cultured according to their recommendations. Briefly, 2.5 10^3 to 2 10^4 cells per well were seeded in 48-well plates 24 hours before drug addition. Cells were treated with 0 to 200 μM (11 concentrations) of compound solubilized in DMSO, adjusting the final concentration of DMSO to 1% in the well. Six days after treatment, the medium was replaced by PBS containing 0.5 mg/ml MTT (Sigma) and cells were incubated for 1-3 hours at 37°C before solubilization of formazan crystals in 100% DMSO. Absorbance was measured using a spectrophotometer at a wavelength of 550nm. Data was analyzed using the GraphPad Prism software (GraphPad Software, Inc., San Diego, USA), and IC50 (dose leading to 50% cell death) was calculated from the dose-response curves.

Anchorage-independent cell growth assay in soft agar

In order to evaluate the effect of one compound on the capacity of tumour cells to grow without anchorage, HCT116 cells were seeded in soft agar. In contrast to microplate assays which average the drug's effects over an entire cell population, clonogenic assays offer the possibility of distinguishing cytotoxic agents (i.e., decreased colony number) from cytostatic agents (i.e., decreased colony size without decreased colony number ; Murphy M.J. *et al.*, 1996).

Briefly, 5 10^3 HCT116 cells were resuspended in 300 µl of complete medium containing 0.3% soft-agar (Difco) and different concentrations of compound (8 concentrations ranging from 0 to 30 µM). Cells were then poured on a solidified layer of medium containing 0.5% of soft agar plus the compound at the same concentration as in the upper layer. Cells were incubated for 7 days at 37°C before pictures of each well were taken using a phase contrast microscope (Nikon) and a digital camera (Nikon Coolpix 990). Pictures were subsequently analyzed using a free image analysis software from the NIH (ImageJ) allowing to determine clones size and number.

Data was analyzed using the GraphPad Prism software, and IC50 (dose leading to a 50% decrease of clone size or number) was calculated from dose-response curves. The ratio IC50 clone size/IC50 clone number was then calculated. When this ratio is equal to 1 (IC50 size=IC50 number), the compound is referred to as "cytotoxic". When the ratio is close to 0 (IC50 size<<IC50 number), the compound is referred to as "cytostatic" (Figure 6).

Migration

An essential characteristic of malignant cells is their ability to migrate, invade host tissues and to produce metastases. In order to evaluate the capacity of one compound to affect the ability of tumoral cells to migrate, migration assays were performed using highly invasive tumoral cells MDA-MB-231. This assay was performed using Falcon HTS Fluoroblock inserts. Culture medium containing Fetal Bovine Serum (FBS; which is used as a chemoattractant) was added to the plate wells and 2 10^4 MDA-MB-231 cells resuspended in medium without FBS and with 0.1% BSA were added to each insert well. The compound of interest was added to the medium in both the upper and the lower chambers. Plate were

incubated for 16 hours at 37°C. Following incubation, the medium was removed from the upper chamber and the entire insert plate was transferred to a second 24-well plate containing 4 µg/ml Calcein-AM in medium containing 0.1% BSA. The plates were incubated for one hour at 37°C, rinsed with Hanks Buffered Saline (HBSS). Fluorescence data were collected using Fluoroskan Ascent FL fluorescence plate reader at an excitation wavelength (Ex) of 485 nm and emission wavelength (Em) of 517 nm. Only those labelled cells that passed through the Matrigel layer and the membrane were detected. Data were analyzed using the GraphPad Prism software.

2. Results

The results are divided and presented below according to the optimized chemical moiety: aromatic (indol-1-yl with various substitutions or phenoxy with various substitutions), linker and kojic acid moieties.

2.1. Results for compounds bearing a 5 carbons linker and a protected tetrahydropyranyl Kojic acid moiety with variations around the aromatic moiety (indole and phenoxy compounds)

2.1.1. MTT assay in tumoral and non tumoral cell lines

In order to determine the impact of changing the aromatic moiety on the capacity of the compounds to affect cell viability, MTT assays using three tumoral cell lines (H460, HCT116 & MCF7) were performed as described in the material and methods. IC_{50}s were calculated and the results for best compounds are shown on Figure 7.

In HCT116, it was shown that compounds having the highest effect on cell viability were indolyl compounds: EHT 0823, EHT 0533, EHT 2427, EHT 8617 and EHT 7395 (Figure 7, top). These compounds have IC_{50}s comprised between (1.5 and 4 µM). The best phenoxy compound is EHT 1405 having an IC_{50} of 4

µM. Indoline (EHT 8650) and chloropurine (EHT 0248) display very high IC_{50}s (above 100 µM) showing that these compounds do not significantly affect cell viability.

Interestingly, these results are highly similar in MDA-MB-231 cells (Figure 7, bottom) and in H460 cells (data not shown), showing that the compounds have a similar activity in tissues from various origins (lung, breast and colon).

MTT assays were also performed in non-tumoral cells lines (MRC5 and MCF10A). It was shown that IC_{50}s for EHT 0533 and EHT 0823 were 1 to 10-fold higher in these cell lines as compared to IC_{50}s obtained in tumoral cell lines H460, HCT116 and MDA-MB-231, showing that our compounds preferentially affect the viability of tumoral cell lines as compared to non-tumoral cell lines (data not shown).

2.1.2. <u>Anchorage-independent growth assay</u>

In order to study the effects of the compounds on the ability of HCT116 cells to grow independently from anchorage, cells were grown in soft agar in the presence of various concentrations of the compounds. These experiments allowed 1) to rank the compounds according to their potential in affecting the clone size and 2) to evaluate their mode of action (cytotoxic *vs* cytostatic).

EHT 2427, EHT 0823, EHT 7395 and EHT 0533 all affect the ability of HCT116 to grow independently from anchorage in the micromolar range. IC_{50}s are very similar to IC_{50}s calculated for reference compound L651582 (Figure 8).

In addition, in our experiments, L651582 was shown to preferentially affect clone size as compared to clone number (ratio IC50 clone size/IC50 clone number = 0.3; Figure 9). This is in accordance with the literature where L651582 is described as a cytostatic compound (Wasilenko et al, 1996). In the contrary, indolyl compounds that were tested affect both clone size and number in a very

similar extent (0.5 < IC50 clone size/IC50 clone number < 0.7). In conclusion, the indolyl compounds have a cytotoxic mode of action.

2.1.3. Migration assay

The indolyl compound EHT 0823 was tested through migration assay, in parallel with reference compound L651582, which is described in the literature as an anti-migratory compound (Kohn EC et al, 1990; Rust WL et al, 2000). Results are presented in Figure 10.

In our system, 10 µM L651582 was shown to decrease the migration of MDA-MB-231 cells of about 40%. Complete inhibition was obtained with 50 µM of compound. No significant inhibition of the cell migration was observed with 10 µM EHT 0823. 90% inhibition was observed with 50 µM EHT 0823. EHT 0823 was shown to be able to affect MDA-MB-231 cell migration, although less efficiently as compared to reference compound L651582.

2.2. Results for non substituted indol-1-yl compounds bearing a protected tetrahydropyranyl Kojic acid moiety having variations around the linker moiety

In order to determine the impact of changing the length of the linker moiety on the capacity of the compounds to alter cell viability, MTT assays using three different tumoral cell lines were performed. IC50s were calculated and the results for best compounds are shown on Figure 11. For more clarity, the compounds were divided in three categories: linear unconstrained (2 to 8 carbons; EHT 7599, EHT 4283, EHT 5741, EHT 7395, EHT 2358, EHT 8733, EHT 2271), xylenyl (spacing equivalent to 4 to 6 carbons; EHT 4336, EHT 8589, EHT 3986) and unsaturated (4 carbons; EHT 6895).

The results show that there is a direct correlation between the linker length and the inhibitory activity of the compounds on the tumoral cell viability (decrease of the IC_{50} value from 2 to 5 carbons, and increase of the IC_{50} value from 5 to 8 carbons). This is true for both constrained and unconstrained linkers. We could also observe that IC_{50}s for compounds with unconstrained linkers were 2-fold lower to IC_{50}s for compounds with constrained (xylenyl or unsaturated) linkers. The 5 carbon linear unconstrained linker is the optimal structure among the structures studied.

2.3. <u>Results for compounds bearing a non substituted indolyl moiety, a 5 carbon atoms linker and having variations around the kojic acid moiety</u>

It was demonstrated that O-THP protected compounds have an antitumoral activity higher as compared to the antitumoral activity of OH unprotected compounds (both through MTT and soft agar assays; data not shown). However, the O-THP protection increases the cLogP of the compounds and consequently decreases their solubility. A new study was initiated in order to identify residues that could replace the O-THP protection, decreasing the cLogP value without affecting the compound's anti-tumoral activity.

For this purpose, MTT assays using HCT116 tumoral cell line was performed. The following residues were tested: benzoyl (EHT 6517), cyclohexanecarboxylate (EHT 2253), ethylcarbamate (EHT 1120), cyclohexylcarbamate (EHT 6231), phenylcarbamate (EHT 4902), and furoate (EHT 4167) derivatives. The reference compound was EHT 7395. Results are shown on Figure 12.

It was shown that the best option was the cyclohexylcarbamate residue, EHT 6231 having an IC_{50} only 2-fold higher as compared to compound EHT 7395.

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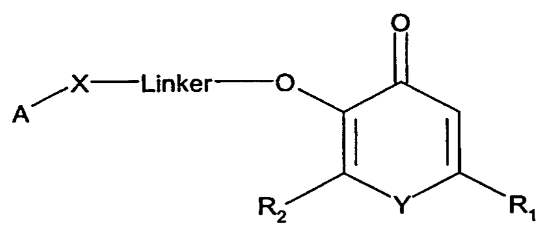
CLAIMS

1- A compound having a general formula (I) :

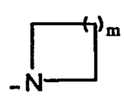


(I)

wherein:

R_1 is CH_2R_3 or COR_3;

R_2 represents a hydrogen atom or an alkenyl group containing from 3 to 6 carbon atoms;

R_3 is -OH, $-OR_4$, $-SR_4$, $-NR_5R_6$, or  ;

R_4 represents a group selected from alkyl containing from 1 to 6 carbon atoms, a cycloalkyl group a radical $-CONR_5R_6$, aryl, a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero- atoms selected from oxygen, sulfur and nitrogen, heteroaryl, aralkyl, heteroaralkyl, alkanoyl or cycloalkanoyl from 2 to 6 carbon atoms, arylcarbonyl, heteroarylcarbonyl, arylalkanoyl and heteroarylalkanoyl;

R_5 and R_6, independently from each other, are selected from a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl;

m is 2 or 3;

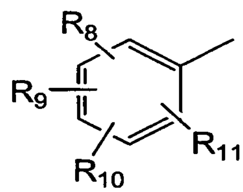
"linker" represents $(CH_2)_n$, wherein n represents an integer between 1 and 10 inclusive or a xylenyl group;

Y represents an oxygen atom, a sulfur atom or a radical $-NR_7-$;

R_7, identical or different, is selected from a group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl;

- either:

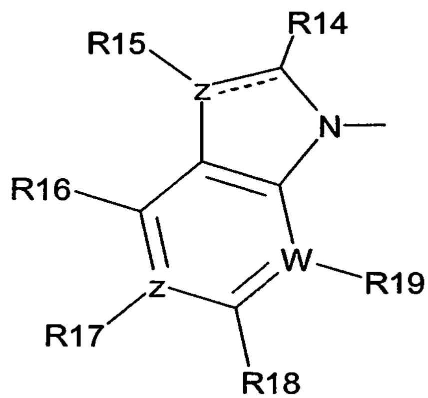
X represents an oxygen atom, a sulfur atom or a radical $-NR_7-$;
A represents either a substituted phenyl group of formula



in which:
R_8, R_9, R_{10} and R_{11}, independently from each other, are selected from a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a $(C_1$-$C_{10})$alkyl group, an alkenyl group, an $(C_1$-$C_{10})$alkanoyl group, a $(C_1$-$C_{10})$alkoxy group, a $(C_1$-$C_{10})$alkoxycarbonyl group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, a $-NHCO(C_1$-$C_6)$alkyl group, $-NO_2$, -CN, a $-NR_{12}R_{13}$ group or a trifluoro$(C_1$-$C_6)$alkyl group; preferably R_8, R_9, R_{10} and R_{11}, not being simultaneously hydrogen atom,
or alternatively two substituents, R_8 and R_9, may form together a mono- or poly-cyclic hydrocarbon group with the carbon atoms of the phenyl group they are attached and the two other substituents, R_{10} and R_{11}, are as defined above;
or A represents a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero-atoms selected from oxygen, sulfur and nitrogen, said ring is bonded directly to X;

R_{12} and R_{13}, independently from each other, are selected in the group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl;

- or X-A represents a group of formula (II):



wherein:

R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, independently from each other, represent a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, $-NO_2$, -CN, a $-NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group, R_{12} and R_{13} being as defined above; alternatively, R_{14} and R_{15} may form together with the bond they are attached thereto a cycloalkyl group (preferably a cyclohexyl group) or an aryl group (preferably a phenyl group);

W represents a carbon or nitrogen atom;

Z represents a carbon or nitrogen atom;

With the provisos that:

- when X and Y are oxygen atoms, A is a phenyl group, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 5 and R_8 on the ortho position on the phenyl

group vis-à-vis X is n-propyl group, then at least one R_9, R_{10} and R_{11} is different from hydrogen;

- when X and Y are oxygen atoms, A is a phenyl group, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 5, R_8 on the ortho position on the phenyl group vis-à-vis X is n-propyl group, R_9 on the meta position vis-à-vis X is an hydroxyl group, and R_{10} on the para position vis-à-vis X is an acetyl group; then R_{11} is different from hydrogen;
- when X and Y are oxygen atoms, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 2 or 3, then A is different from a non-substituted naphthalene group;

its tautomers, optical and geometrical isomers, racemates, salts, hydrates and mixtures thereof.

2- A compound according to claim 1, wherein:

- X is oxygen or sulfur; and/or
- Y is oxygen; and/or
- linker is $(CH_2)_n$, wherein, n is from 4 to 7 inclusive or a xylenyl group (meta, para, or ortho); and/or
- R_1 is $-CH_2OH$, $-CH_2$-O-benzyl, $-CH_2$-O-tetrahydropyran, $-CO_2H$ or -CO-NH-benzyl; and/or
- R_2 is a hydrogen atom, a propen-1-yl group, a propen-2-yl group ; and/or
- A is a substituted phenyl as defined above, a pyridine group (preferably pyridin-2-yl group), a furan or a thiophene group, optionally substituted.

3- A compound according to claim 2, wherein A is a phenyl substituted by at least one halogen atom, preferably chlorine.

4- A compound according to one of the preceding claims, wherein A is a phenyl group substituted with at least two substituents simultaneously represent Cl.

5- A compound according to one of the preceding claims, wherein A is a substituted, at least one of the substituents on the phenyl group is a halogen

atom, an alkyl group (preferably propyl) or an alkenyl (preferably propenyl), a trifluoroalkyl group (trifluoromethyl group), $-NO_2$, -CN, an alkoxy group (preferably methoxy or butoxy, optionnally substituted with a cycloalkyl group (preferably cyclopropyl), an alkoxycarbonyl group (preferably $-COOC_2H_5$), a alkanoyl group (preferably acetyl), a $-NR_{12}R_{13}$ group, preferably wherein R_{12} is H and R_{13} is hydrogen or an alkyl group (more preferably ethyl group), or a $-NHCO(C_1-C_6)$alkyl group (preferably $-NHCOCH_3$).

6. A compound according to one of the preceding claims, wherein A is a substituted phenyl, R_8 represents a hydrogen atom, a propyl group or an ethoxy group, R_9 and R_{10} represent a hydrogen atom, or an halogen atom, preferably chlorine, and R_{11} is a hydrogen atom.

7. A compound according to claim 1 or 2, wherein A is a substituted pyridine (preferably pyridin-2-yl), the pyridin is substitued with at least a halogen atom, preferably chlorine, and/or trifluoroalkyl (preferably trifluoromethyl).

8. A compound according to claim 1 or 2, wherein A is a substituted thiophene, the thiophene is substitued with at least a halogen atom, preferably bromine, and/or an alkoxycarbonyl group (preferably $-COOCH_3$).

9. A compound according to claim 1 or 2, wherein A is a substituted furan, the furan is substitued with at least one, or more specifically two, alkyl group (preferably CH_3).

10. A compound according to claim 1, wherein X-A represents a group of formula (II) as identified above,

- W and z represent a carbon atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}, or
- W represents a nitrogen atom, z represents a carbon atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}, or

- W and z represent a carbon atom and a single bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}, or
- W and z represent a nitrogen atom atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}.

11. A compound according to the preceding claim, wherein X-A represents a group of formula (II), wherein W and z represent a carbon atom and a double bond is present between the carbon atoms of the cycle supporting R_{14} and R_{15}.

12. A compound according to one of the preceding claims 1, 10 and 11, wherein X-A represents a group of formula (II) as identified in claim 1 and wherein:

- Y is oxygen; and/or
- linker is $(CH_2)_n$, wherein, n is from 2 to 8 inclusive, preferably 5, or a xylenyl group; and/or
- R_1 is $-CH_2OH$, $-CH_2OCONR_5R_6$, wherein R_5 is preferably H and R6 is preferably ethyl, cyclohexyl, phenyl, optionally substituted with halogen atom (preferably Cl) or with NO2, -CH2OCO-alkyl (preferably propyl), -CH2OCO-cycloalkyl (wherein preferably cycloalkyl is cyclohexyl), $-CH_2$-O-CO-benzyl, $-CH_2$-O-CO-aryl (wherein aryl is preferably phenyl or furan), $-CH_2$-O-tetrahydropyran, $-CO_2H$ or -CO-NH-benzyl; and/or
- R_2 is a hydrogen atom, a propen-1-yl group, a propen-2-yl group.

13. A compound according to one the preceding claims 1, 10-12, wherein X-A is the group of formula (II) and R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, independently from each other, represent a hydrogen atom, a aryl group (preferably a phenyl group), an alkyl group (preferably a methyl group), an alkoxy group (preferably a methoxy group), a halogen atom (preferably Cl or F).

14. A compound according to one the preceding claims 1, 10-12, wherein X-A is the group of formula (II), R_{14} and R_{15} form together with the bond they are attached thereto a cycloalkyl group (preferably a cyclohexyl group) or an aryl

group (preferably a phenyl group) and R_{16}, R_{17}, R_{18} and R_{19}, independently, represent preferably a hydrogen atom and/or an alkyl group.

15. A compound according to one the preceding claims 1, 10-12, wherein X-A is the group of formula (II), R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19} represent a hydrogen atom.

16- A compound according to claim 1, which is chosen in the group consisting of:
5-[5-(4-Chlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[5-(3-Chlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[5-(3,4-Dichlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[4-(3,4-Dichlorophenyloxy)butyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[5-(4,5-Dichloro-2-propylphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[5-(2-Ethyloxyphenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[6-(3,4-Dichloro-2-propylphenyloxy)hexyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[7-(3,4-Dichloro-2-propylphenyloxy)heptyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[9-(3,4-Dichlorophenyloxy)nonyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
2-(Benzyloxymethyl)-5-[5-(3,4-dichlorophenyloxy)pentyloxy]-2-(hydroxymethyl)-4*H*-pyran-4-one
5-[5-(4-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid
5-[5-(3-Chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid
5-[5-(3,4-Dichlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid
5-[4-(3,4-Dichlorophenyloxy)butyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid
5-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid
5-[5-(2-Ethyloxyphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxylic acid

N-Benzyl-5-[5-(4-chlorophenyloxy)pentyloxy]-4-oxo-4*H*-pyran-2-carboxamide

(E)-3-[5-(4-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)-3-[5-(3-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)-3-[5-(3,4-Chlorophenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)-3-[5-(3,4-Chloro-2-propylphenyloxy)pentyloxy]-6-(hydroxymethyl)-2-(propen-1-yl)-4*H*-pyran-4-one

(E)- 6-(Hydroxymethyl)-2-(propen-1-yl)-3-[5-(2-propylphenyloxy)pentyloxy]-4*H*-pyran-4-one

(E)- 3-[5-(4-Chlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(E)- 3-[5-(3-Chlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(E)- 3-[5-(3,4-Dichlorophenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(E)- 3-[5-(3,4-Dichloro-2-propylphenyloxy)pentyloxy]-2-(propen-1-yl)-4-oxo-4*H*-pyran-6-carboxylic acid

(E)- 2-(Propen-1-yl)-3-[5-(2-propylphenyloxy)pentyloxy]-4-oxo-4*H*-pyran-6-carboxylic acid

2-Fluoro-4-[5-(6-hydroxymethyl-4-oxo-4*H*-pyran-3-yloxy)-pentyloxy]-benzonitrile (EHT 2904)

5-[5-(2-Allyl-4-chloro-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 5431)

5-[5-(4-Chloro-2-propyl-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 6152)

5-[5-(2-Allyl-3,5-dichloro-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 6978)

5-[5-(3,5-Dichloro-2-propyl-phenoxy)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT2991)

(*E*)-3-[5-(3,5-Bis-trifluoromethyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 5403)

(*E*)-3-[5-(3,4-Difluoro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 8307)

(*E*)-2-Fluoro-4-[5-(6-hydroxymethyl-4-oxo-2-propenyl-4*H*-pyran-3-yloxy)-pentyloxy]-benzonitrile (EHT 4112)

(*E*)-3-[5-(2-Allyl-4-chloro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 9226)

(*E*)- 3-[5-(4-Chloro-2-propyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 1405)

(*E*)-3-[5-(2-Allyl-3,5-dichloro-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 6506)

(*E*)-3-[5-(3,5-Dichloro-2-propyl-phenoxy)-pentyloxy]-6-hydroxymethyl-2-propenyl-4*H*-pyran-4-one (EHT 9916)

2-Hydroxymethyl-5-(5-indol-1-yl-pentyloxy)-4*H*-pyran-4-one (EHT 6353)

Ethyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 1120)

Cyclohexyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 6231)

Phenyl-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 4902)

(4-Chloro-phenyl)-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2232)

(4-Nitro-phenyl)-carbamic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 5332)

Butanoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 1393)

Cyclohexanecarboxylic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2253)

Phenyl-acetic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 2665)

Benzoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 6517)

Furan-3-carboxylic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 4167)

4-Chloro-benzoic acid 5-(5-indol-1-yl-pentyloxy)-4-oxo-4*H*-pyran-2-ylmethyl ester (EHT 0078)

(*E*)-6-Hydroxymethyl-3-(5-indol-1-yl-pentyloxy)-2-propenyl-4*H*-pyran-4-one (EHT 7286)

5-(5-Indol-1-yl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7395)

5-(5-Phenylsulfanyl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 1414)

2-Hydroxymethyl-5-(5-phenylsulfanyl-pentyloxy)-4*H*-pyran-4-one (EHT 2939)

5-(5-Phenoxy-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6245)

2-Hydroxymethyl-5-(5-phenoxy-pentyloxy)-4*H*-pyran-4-one (EHT 1329)

5-[5-(5-Chloro-pyridin-2-yloxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0696)

5-[5-(5-trifluoromethyl-pyridin-2-yloxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 1171)

5-[5-(3,4-Dimethoxy-phenylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 3663)

4-Bromo-3-{5-[4-oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-thiophene-2-carboxylic acid methyl ester (EHT 4408)

3-Cyclopropylmethoxy-4-{5-[4-oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-benzoic acid ethyl ester (EHT 7565)

5-[5-(4-Butoxy-3-nitro-phenylamino)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5230)

5-[5-(4-Acetyl-3-ethylamino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9411)

N-(3-{5-[4-Oxo-6-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-3-yloxy]-pentyloxy}-4-propyl-phenyl)-acetamide (EHT 7151)

5-[5-(6-Acetyl-3-ethylamino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7096)

5-[5-(2-Phenyl-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9013)

5-[5-(4-Acetyl-3-amino-2-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5769)

5-[5-(2,5-Dimethyl-furan-3-ylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7976)

5-[5-(2,4-Dimethyl-pyrido[2,3-*b*]indol-9-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6448)

5-[5-(2-Methyl-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2427)

5-(5-Pyrrolo[2,3-b]pyridin-1-yl-pentyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8309)

5-[5-(5,6-Dimethoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5457)

5-[5-(6-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5235)

5-[5-(6-Chloro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8617)

5-[5-(4-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0091)

5-[5-(5-Methoxy-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8140)

5-[5-(2,4-Dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-*b*]indol-9-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 7337)

5-[5-(3,4-Dichloro-phenylsulfanyl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0407)

5-[5-(5-Chloro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0823)

5-[5-(5-Fluoro-indol-1-yl)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 0533)

5-[5-(2-Methoxy-4-propyl-phenoxy)-pentyloxy]-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 9387)

5-[2-Indol-1-yl-ethoxy)-2-(tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 7599)

5-(3-Indoyl-1-yl-propoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 4283)

5-(4-Indol-1-yl-butoxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 5741)

2-Hydroxymethyl-5-(4-indol-1-yl-butoxy)-4*H*-pyran-4-one (EHT 3089)

5-(4-Indol-1-yl-(*trans*)-but-2-enyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 6895)

2-Hydroxymethyl-5-(5-indol-1-yl-pentyloxy)-4*H*-pyran-4-one (EHT 6353)

5-(5-Indol-1-yl-hexyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2358)

5-(8-Indol-1-yl-heptyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 8733)

5-(8-Indol-1-yl-octyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 2271)

5-[5-(5-Chloro-indol-1-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 9238)

5-[5-(2,3-Dihydro-indol-1-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 8650)

5-[5-(6Chloro-purin-9-yl)-pentyloxy]-2-hydroxymethyl-4*H*-pyran-4-one (EHT 0248)

2-Hydroxymethyl-5-[5-(3-methyl-indol-1-yl)-pentyloxy]-4*H*-pyran-4-one (EHT 3065)

5-[5-(5-fluoro-indol-1-yl)-pentyloxy]-2-Hydroxymethyl-4*H*-pyran-4-one (EHT 9546)

5-[5-(6-chloro-indol-1-yl)-pentyloxy]-2-Hydroxymethyl-4*H*-pyran-4-one (EHT 9853)

5-[3-Indol-1-yl-methyl-benzyloxy)-2-tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 8589)

5-[4-Indol-1-yl-methyl-benzyloxy)-2-tetrahydro-pyran-2-yloxymethyl)]-4*H*-pyran-4-one (EHT 3986)

5-(2-Indol-1-ylmethyl-benzyloxy)-2-(tetrahydro-pyran-2-yloxymethyl)-4*H*-pyran-4-one (EHT 4336).

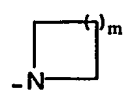
17- A pharmaceutical composition comprising at least one compound according to any one of the preceding claims and a pharmaceutically acceptable vehicle or support.

18- A composition according to the preceding claim, for the treatment of a disease associated with abnormal cell proliferation.

19- A use of an effective amount of at least one compound of formula (I) as defined in one of the preceding claims 1-16 for the preparation of a pharmaceutical composition for the treatment of a disease associated with abnormal cell proliferation, wherein:

R_1 is CH_2R_3 or COR_3;

R_2 represents a hydrogen atom or an alkenyl group containing from 3 to 6 carbon atoms;

R_3 is -OH, $-OR_4$, $-SR_4$, $-NR_5R_6$, or  ;

R_4 represents a group selected from alkyl containing from 1 to 6 carbon atoms, a cycloalkyl group a radical $-CONR_5R_6$, aryl, a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero- atoms selected from oxygen, sulfur and nitrogen, heteroaryl, aralkyl, heteroaralkyl, alkanoyl or cycloalkanoyl from 2 to 6 carbon atoms, arylcarbonyl, heteroarylcarbonyl, arylalkanoyl and heteroarylalkanoyl;

R_5 and R_6, independently from each other, are selected from a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl;

m is 2 or 3;

"linker" represents $(CH_2)_n$, wherein n represents an integer between 1 and 10 inclusive or a xylenyl group (meta, para or ortho);

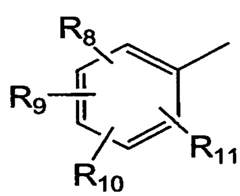
Y represents an oxygen atom, a sulfur atom or a radical $-NR_7-$;

R_7, identical or different, is selected from a group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl;

- either:

X represents an oxygen atom, a sulfur atom or a radical $-NR_7-$;

A represents either a substituted phenyl group of formula



in which:

R_8, R_9, R_{10} and R_{11}, independently from each other, are selected from a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an alkenyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, a (C_1-C_{10})alkoxycarbonyl group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, a $-NHCO(C_1-C_6)$alkyl group, $-NO_2$, $-CN$, a $-NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group; preferably R_8, R_9, R_{10} and R_{11}, not being simultaneously hydrogen atom,

or alternatively two substituents, R_8 and R_9, may form together a mono- or poly-cyclic hydrocarbon group with the carbon atoms of the phenyl group they are attached and the two other substituents, R_{10} and R_{11}, are as defined above;

or A represents a 5- to 12- membered heterocyclic ring which has 1 to 3 hetero-atoms selected from oxygen, sulfur and nitrogen, said ring is bonded directly to X;

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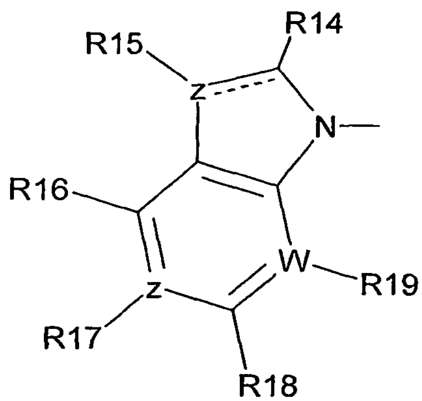
R_{12} and R_{13}, independently from each other, are selected in the group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl and an aralkyl ;

- or X-A represents a group of formula (II):



wherein:

R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, independently from each other, represent a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a (C_1-C_{10})alkyl group, an (C_1-C_{10})alkanoyl group, a (C_1-C_{10})alkoxy group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, -NO_2, -CN, a -$NR_{12}R_{13}$ group or a trifluoro(C_1-C_6)alkyl group, R_{12} and R_{13} being as defined above; alternatively, R_{14} and R_{15} may form together with the bond they are attached thereto a cycloalkyl group (preferably a cyclohexyl group) or an aryl group (preferably a phenyl group);

W represents a carbon or nitrogen atom;

Z represents a carbon or nitrogen atom.

20- A use according to claim 19, wherein diseases associated with abnormal cell proliferation are cancers and restenosis.

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21. A use according to claim 20, wherein the cancer is selected from prostate cancer, ovarian cancer, pancreas cancer, lung cancer, breast cancer, liver cancer, head and neck cancer, colon cancer, bladder cancer, non-Hodgkin 's lymphoma cancer and melanoma.

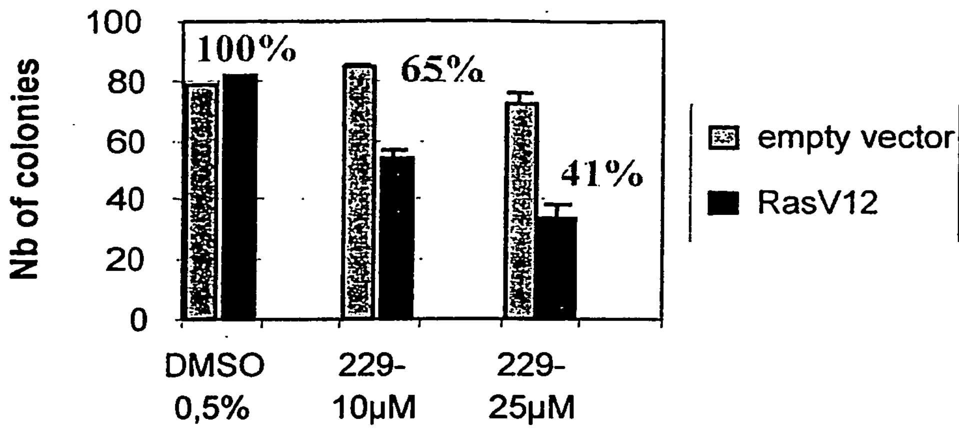


FIGURE 1

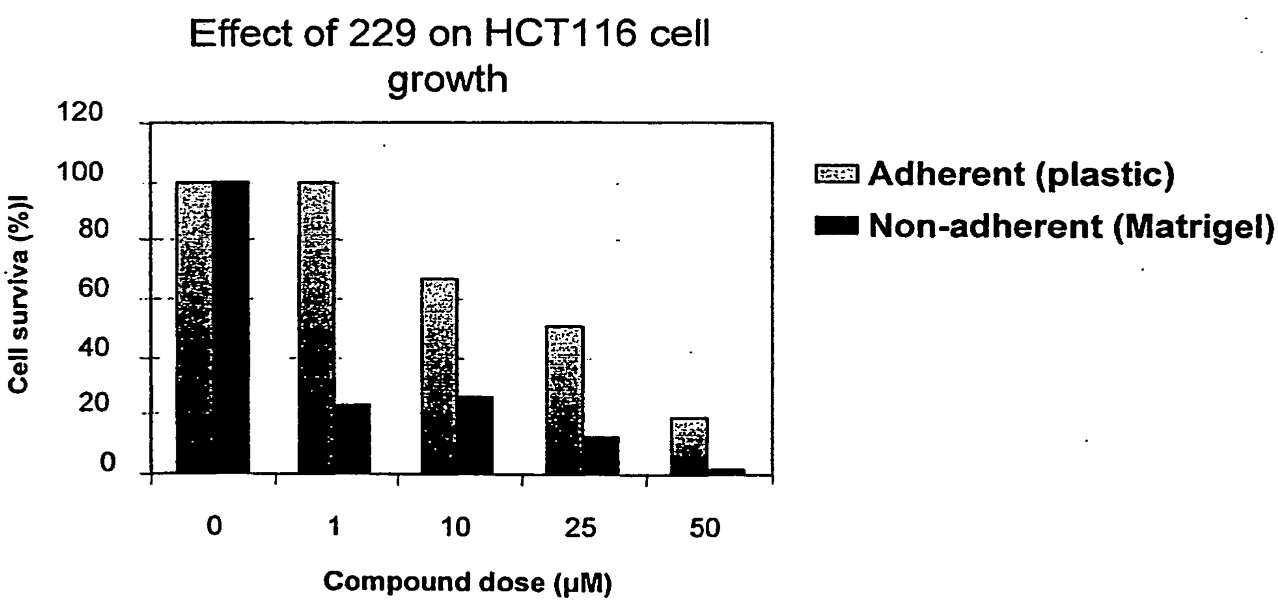


FIGURE 2

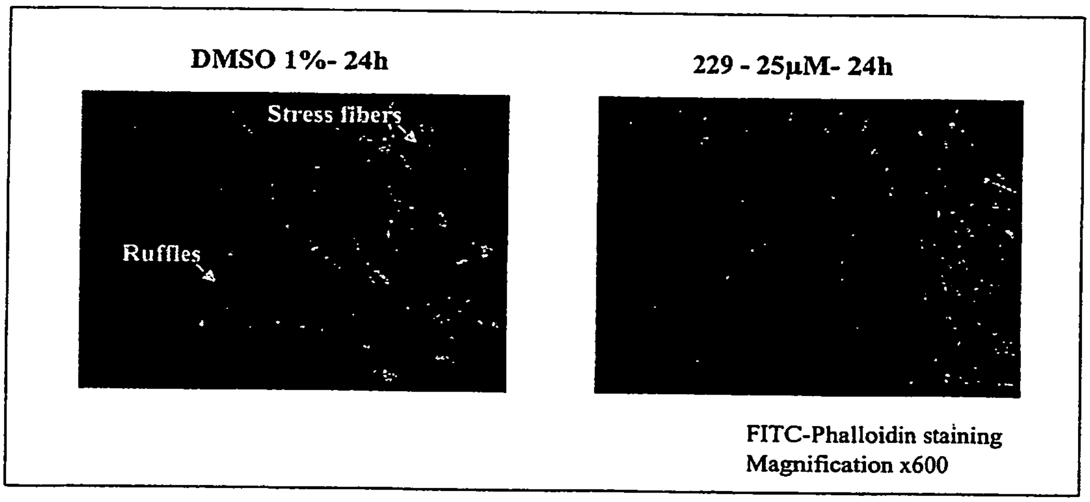

DMSO 1%- 24h
229 - 25µM- 24h
Stress fibers
Ruffles
FITC-Phalloidin staining
Magnification x600

FIGURE 3

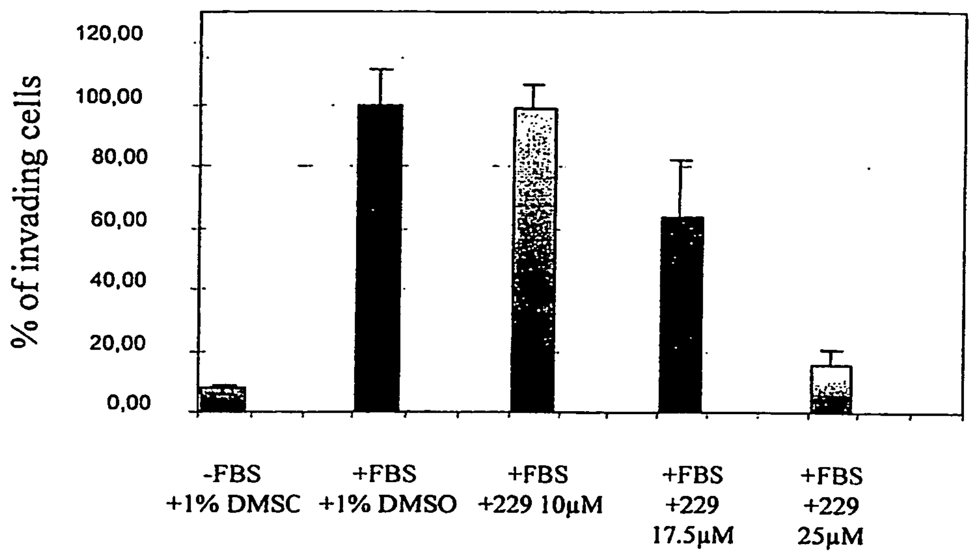


FIGURE 4

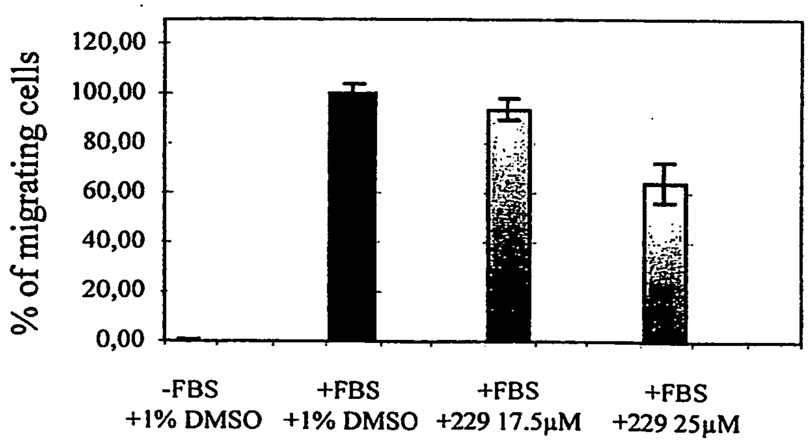
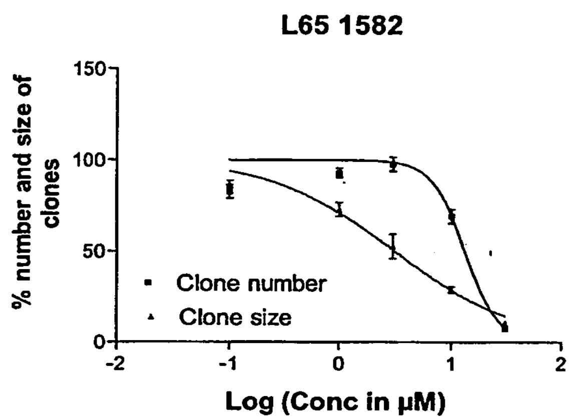


FIGURE 5


L65 1582
% number and size of clones
150
100
50
0
-2
-1
0
1
2
Log (Conc in μM)
Clone number
Clone size

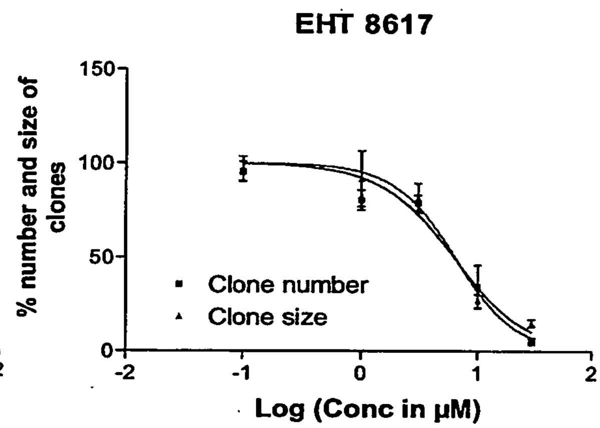
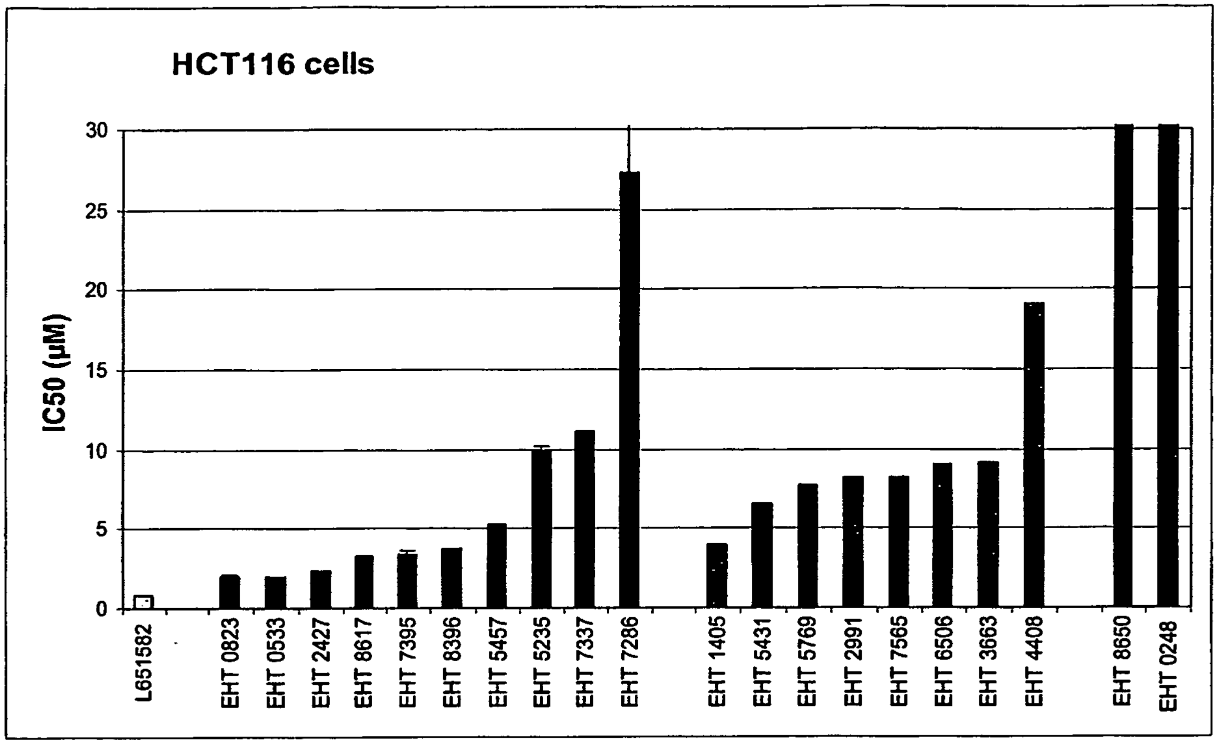

EHT 8617
% number and size of clones
150
100
50
0
-2
-1
0
1
2
Log (Conc in μM)
Clone number
Clone size

FIGURE 6


HCT116 cells
IC50 (µM)
30
25
20
15
10
5
0
L651582
EHT 0823
EHT 0533
EHT 2427
EHT 8617
EHT 7395
EHT 8396
EHT 5457
EHT 5235
EHT 7337
EHT 7286
EHT 1405
EHT 5431
EHT 5769
EHT 2991
EHT 7565
EHT 6506
EHT 3663
EHT 4408
EHT 8650
EHT 0248

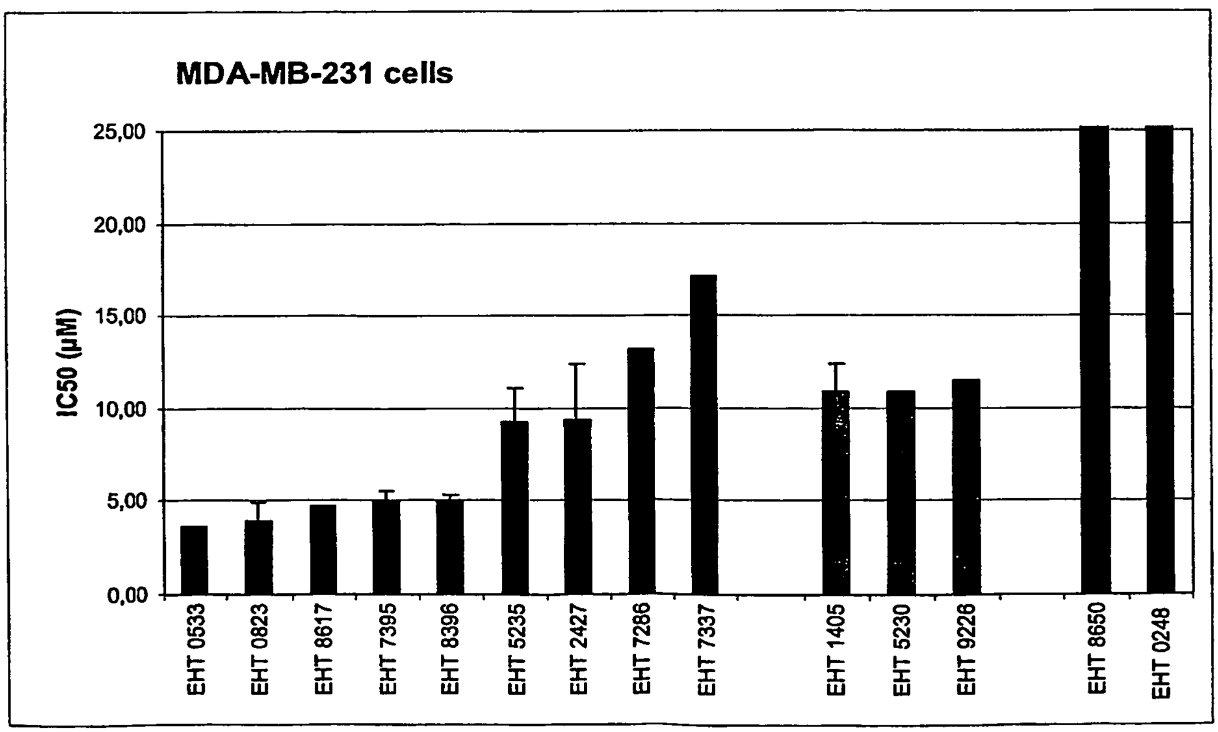

MDA-MB-231 cells
IC50 (µM)
25,00
20,00
15,00
10,00
5,00
0,00
EHT 0533
EHT 0823
EHT 8617
EHT 7395
EHT 8396
EHT 5235
EHT 2427
EHT 7286
EHT 7337
EHT 1405
EHT 5230
EHT 9226
EHT 8650
EHT 0248

FIGURE 7

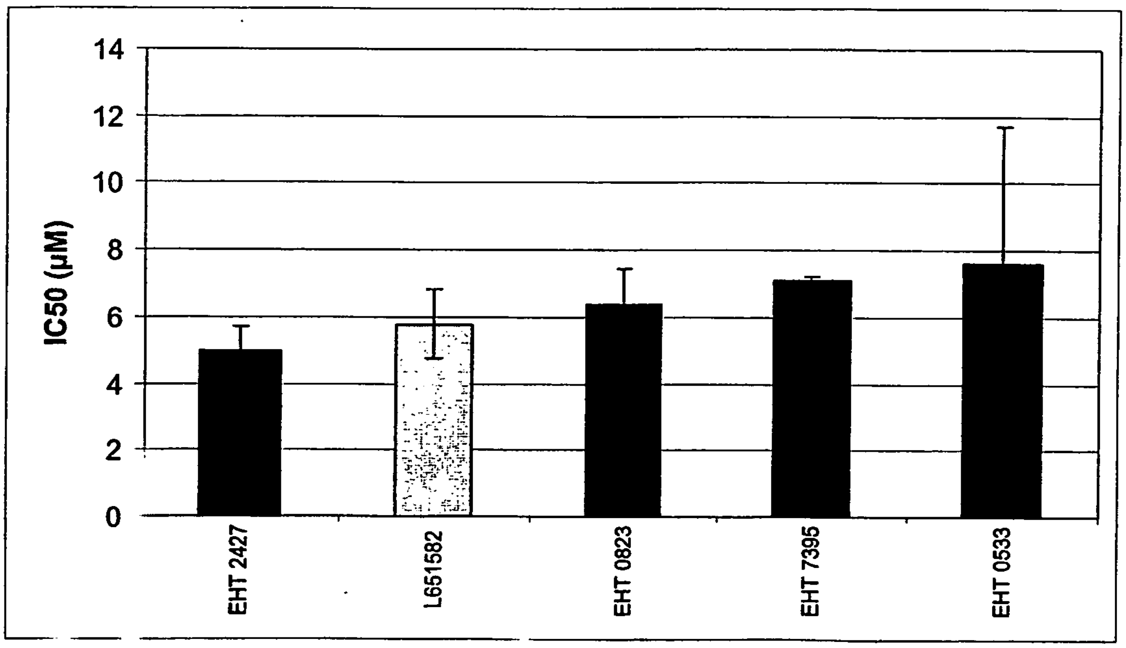

14
12
10
8
6
4
2
0
IC50 (µM)
EHT 2427
L651582
EHT 0823
EHT 7395
EHT 0533

FIGURE 8

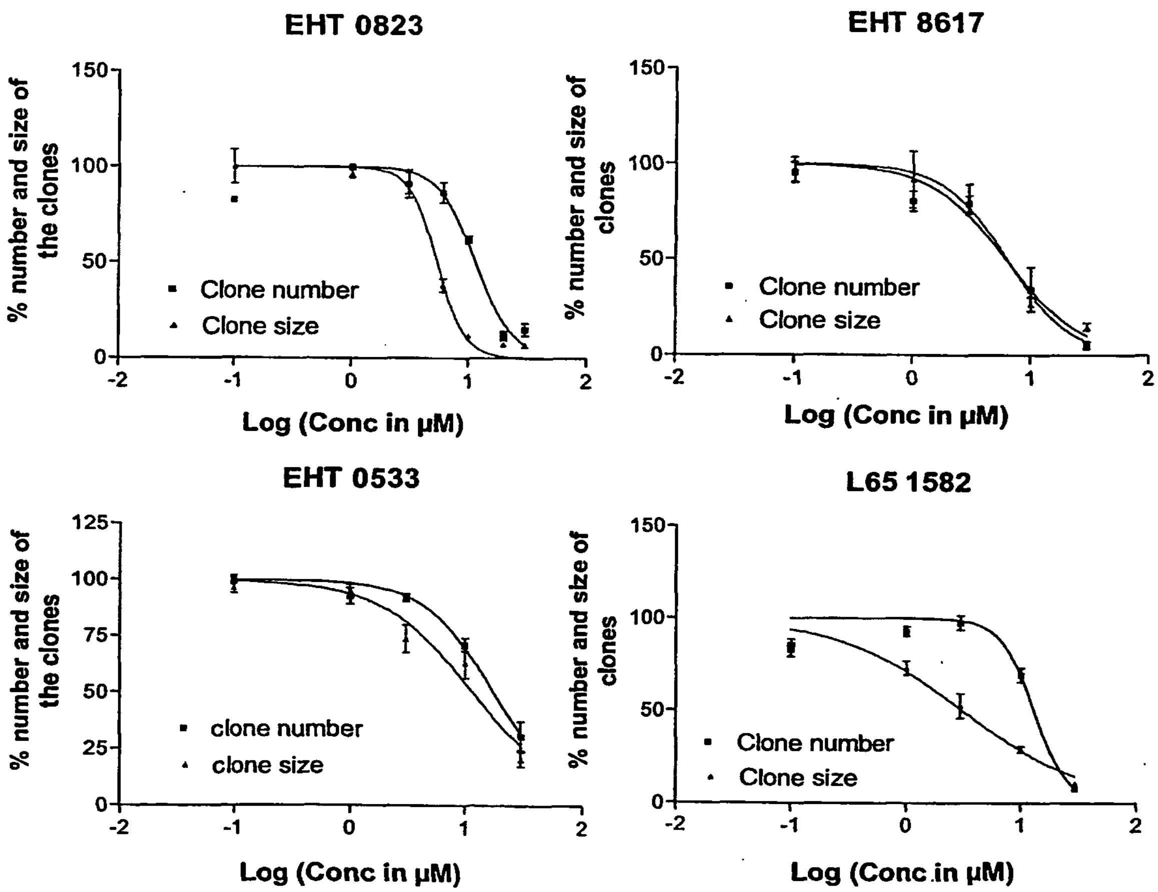
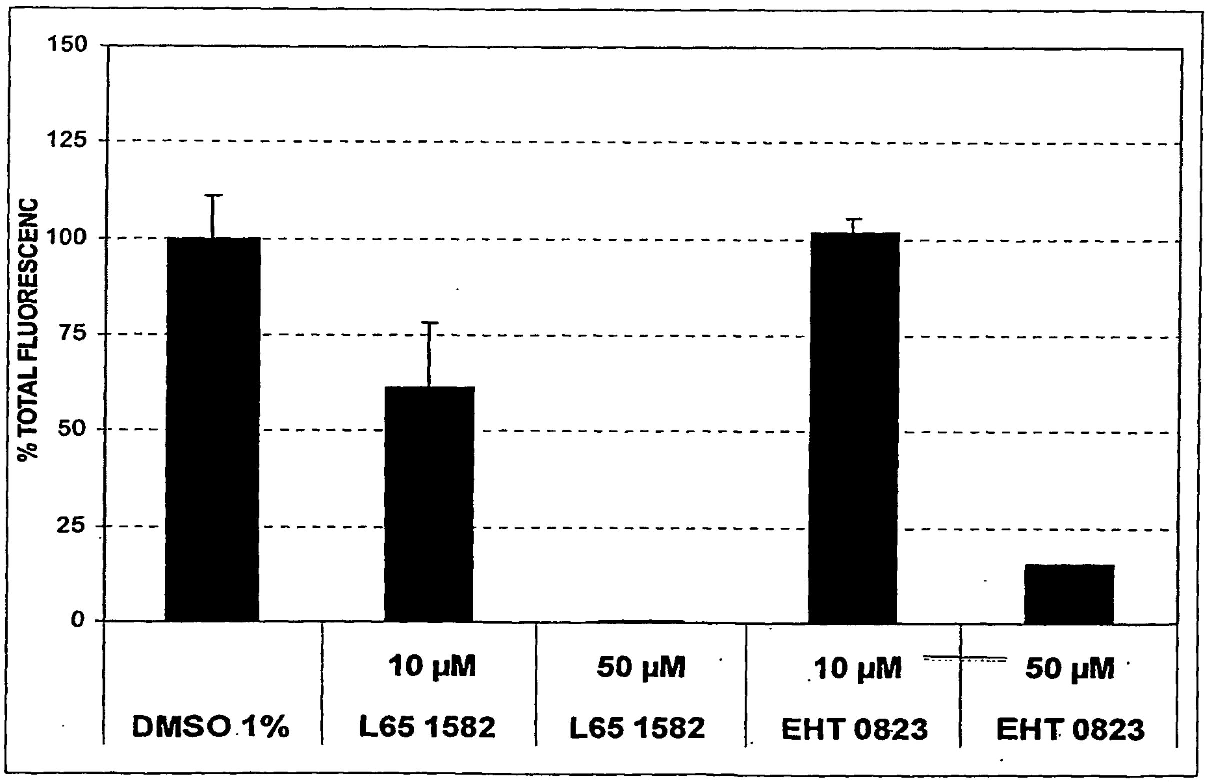

EHT 0823
% number and size of the clones
Clone number
Clone size
Log (Conc in μM)
EHT 8617
% number and size of clones
Clone number
Clone size
Log (Conc in μM)
EHT 0533
% number and size of the clones
clone number
clone size
Log (Conc in μM)
L65 1582
% number and size of clones
Clone number
Clone size
Log (Conc in μM)

FIGURE 9



150
125
100
75
50
25
0
% TOTAL FLUORESCENC
DMSO 1%
10 µM L65 1582
50 µM L65 1582
10 µM EHT 0823
50 µM EHT 0823

FIGURE 10

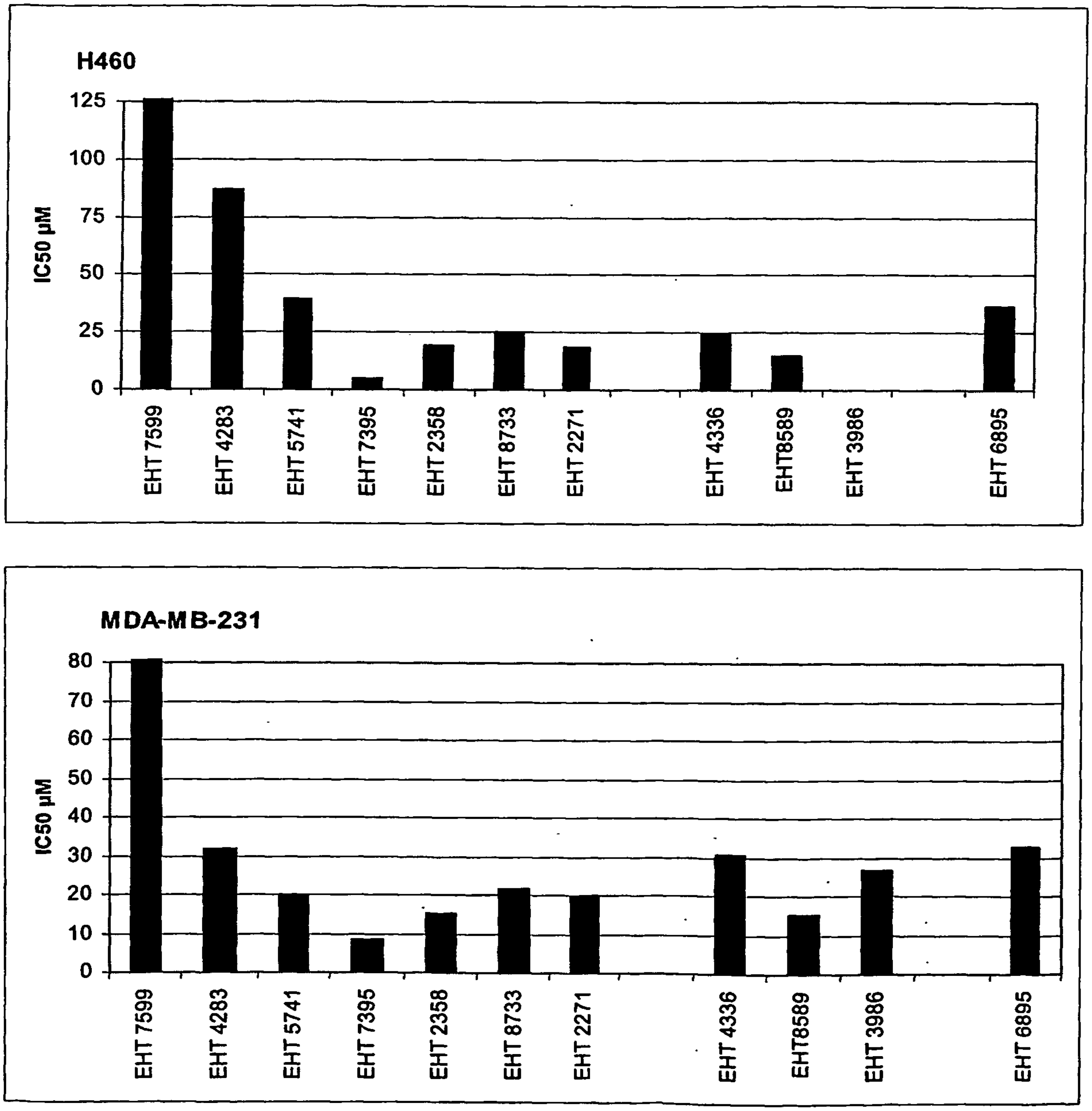

H460
IC50 µM
125
100
75
50
25
0
EHT 7599
EHT 4283
EHT 5741
EHT 7395
EHT 2358
EHT 8733
EHT 2271
EHT 4336
EHT8589
EHT 3986
EHT 6895
MDA-MB-231
IC50 µM
80
70
60
50
40
30
20
10
0
EHT 7599
EHT 4283
EHT 5741
EHT 7395
EHT 2358
EHT 8733
EHT 2271
EHT 4336
EHT8589
EHT 3986
EHT 6895

FIGURE 11

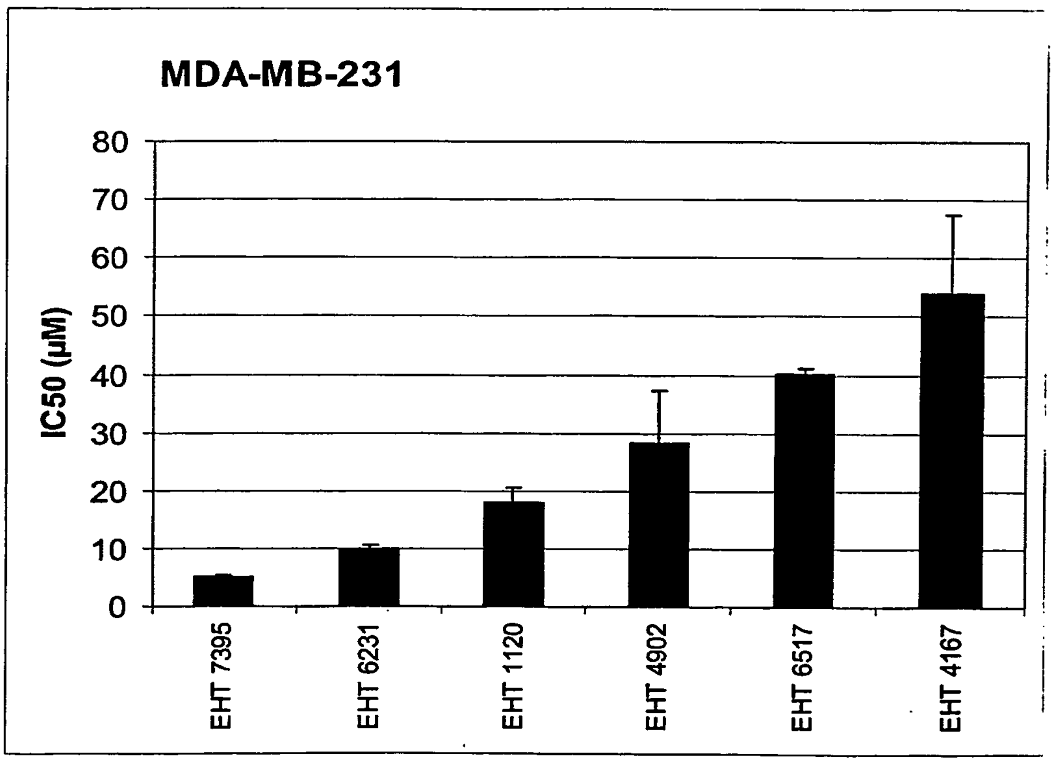

MDA-MB-231
IC50 (µM)
80
70
60
50
40
30
20
10
0
EHT 7395
EHT 6231
EHT 1120
EHT 4902
EHT 6517
EHT 4167

FIGURE 12

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 03/01050

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/38 C07D405/12 C07D405/14 C07D407/12 C07D411/14 C07D407/14 A61K31/351 //(C07D405/12,309:00,209:00), (C07D405/14,309:00,307:00,209:00),(C07D407/12,309:00,309:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 812 584 A (MASATERU MIYANO ET AL) 14 March 1989 (1989-03-14) examples 1-15	1-6, 16-22
X	US 4 705 871 A (MASATERU MIYANO ET AL) 10 November 1987 (1987-11-10) claims 1-4	1-6, 16-22
X	US 4 644 071 A (MASATERU MIYANO ET AL) 17 February 1987 (1987-02-17) claims 1-20	1-22
X	US 4 855 310 A (MURASE KIYOSHI ET AL) 8 August 1989 (1989-08-08) example 6	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2003	23/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goss, I

INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/IB 03/01050

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D405/14,309:00,309:00,213:00),(C07D411/14,333:00,309:00, 309:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

[ ] Further documents are listed in the continuation of box C.

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goss, I

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
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			ES	8801232	A1	01-03-1988
			ES	8801233	A1	01-03-1988
			ES	8801234	A1	01-03-1988
			ES	8801235	A1	01-03-1988
			ES	8801188	A1	01-03-1988
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			KR	9004804	B1	06-07-1990
			PH	22520	A	17-10-1988
			SU	1491337	A3	30-06-1989
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			JP	63035626	B	15-07-1988
			SU	1470186	A3	30-03-1989
			SU	1438610	A3	15-11-1988
			SU	1493105	A3	07-07-1989
			SU	1452481	A3	15-01-1989
			SU	1454249	A3	23-01-1989
			ZA	8508493	A	30-07-1986

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(74) Agents: **BECKER, Philippe** et al.; Cabinet Becker et Associés, 35, rue des Mathurins, F-75008 Paris (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

Date of publication of the amended claims: 27 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/074508 A1

(54) Title: COMPOUNDS AND METHODS OF TREATING CELL PROLIFERATIVE DISEASES

(57) Abstract: The present invention relates to compounds and their uses, particularly in the pharmaceutical industry. The invention discloses compounds having anti-proliferative activities, as well as methods for treating various diseases associated with abnormal cell proliferation, including cancer, by administering said compounds. It further deals with pharmaceutical compositions comprising said compounds, more particularly useful to treat cancers.

AMENDED CLAIMS

[received by the International Bureau on 19 September 2003 (19.09.03); original claim 1 amended; remaining claims unchanged (1 page)]

group vis-à-vis X is n-propyl group, then at least one R_9, R_{10} and R_{11} is different from hydrogen;

- when X and Y are oxygen atoms, A is a phenyl group, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 3 or 5, R_8 on the ortho position on the phenyl group vis-à-vis X is n-propyl group, R_9 on the meta position vis-à-vis X is an hydroxyl group, and R_{10} on the para position vis-à-vis X is an acetyl group; then R_{11} is different from hydrogen;

- when X and Y are oxygen atoms, R_2 is a hydrogen atom, linker is $(CH_2)_n$, wherein n is 2 or 3, then A is different from a non-substituted naphthalene group;

its tautomers, optical and geometrical isomers, racemates, salts, hydrates and mixtures thereof.

2- A compound according to claim 1, wherein:

- X is oxygen or sulfur; and/or
- Y is oxygen; and/or
- linker is $(CH_2)_n$, wherein, n is from 4 to 7 inclusive or a xylenyl group (meta, para, or ortho); and/or
- R_1 is $-CH_2OH$, $-CH_2$-O-benzyl, $-CH_2$-O-tetrahydropyran, $-CO_2H$ or -CO-NH-benzyl; and/or
- R_2 is a hydrogen atom, a propen-1-yl group, a propen-2-yl group ; and/or
- A is a substituted phenyl as defined above, a pyridine group (preferably pyridin-2-yl group), a furan or a thiophene group, optionally substituted.

3- A compound according to claim 2, wherein A is a phenyl substituted by at least one halogen atom, preferably chlorine.

4- A compound according to one of the preceding claims, wherein A is a phenyl group substituted with at least two substituents simultaneously represent Cl.

5- A compound according to one of the preceding claims, wherein A is a substituted, at least one of the substituents on the phenyl group is a halogen